Ethnic differences in Cardiac Adaptation to Exercise

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Abstract

Regular participation intense intense physical activity induces characteristic physiological ECG and echocardiographic changes. These are well described in Caucasian athletes (WA). Male black athletes (MBAs) demonstrate a higher prevalence of repolarisation anomalies and a greater maximal left ventricular wall thickness (mLVWT). The longitudinal significance of this is unclear. There is no published data on female black athletes (FBAs).

Methods

Between 1996 and 2010, 1144 elite BAs (21% female) underwent a standard pre-participation screen, including a 12-lead ECG and 2-D trans-thoracic echocardiogram. These were compared with 2059 similar WAs (12% female), 259 sedentary black controls (BCs; 54% female), and 52 black patients with hypertrophic cardiomyopathy (HCM). Any healthy subject exhibiting a mLVWT of >11mm (females) or >13mm (males), underwent comprehensive examination to look for phenotypic features of HCM. Male athletes were followed up for 69.7±29.6 months.

Results

BAs demonstrated a greater mLVWT (Females 9.2±1.2mm vs. 8.6±1.2mm, P<0.001: Males 10.6 ±1.6mm vs. 10.0±1.2, P<0.001) than WA and BC subjects. Eight FBA (3%) exhibited a mLVWT >11mm (12 to 13mm) compared with none of the FWA. T wave inversions (TWI) were

present in 82.7% of HCM patients, 22.8% MBAs, 14% FBAs, 10.1% BCs, 3.7% MWA and 2% FWA (P<0.001). The major determinant of TWI in healthy subjects was black ethnicity. In BAs, TWI were confined predominately to the anterior leads (V1-4). Anterior TWI were infrequent amongst BCs (4.2%) and HCM patients (3.8%). TWI in the lateral leads were frequently seen amongst HCM patients(79.6%), but rare in all healthy individuals. During follow-up, one MBA survived a cardiac arrest, and two athletes (one MBA and one MWA) were diagnosed with HCM.

Conclusion

Systematic physical exercise in BAs is associated with greater LV hypertrophy and higher prevalence of TWI than in similar WAs. However, a mLVWT >13mm (females) or >16mm (males) or deep TWI in the inferior/lateral leads are rare and warrant investigation.

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List of Abbreviations

A wave - Late diastolic mitral valve inflow peak velocity

A'- Late annular diastolic peak velocity (lateral mitral annulus)

Ao - Aortic annulus diameter

ARVC - Arrhythmogenic Right Ventricular Cardiomyopathy

AV - Atrio-Ventricular node,

BA - Black Athlete

BC - Black Control Subject

BSA - Body Surface Area

CMR - Cardiac Magnetic resonance

DBP - Diastolic Blood Pressure

E wave - Early diastolic mitral valve peak inflow velocity

E:A - Ratio of peak Early diastolic mitral inflow velocity to peak late diastole mitral inflow velocity

E Decel - E wave deceleration time

E`- Early diastolic annular peak velocity (lateral mitral annulus)

E:E` - Ratio of peak early diastolic mitral inflow velocity to peak early diastolic mitral annular velocity

EF - Ejection Fraction

FBA - Female black athlete

FWA - Female White Athlete

HR - Resting Heart rate

HCM - Hypertrophic Cardiomyopathy

ICD - Implantable Cardioverter Defibrillator

IVSd - Maximal left ventricular septal wall thickness in end-diastole

IVRT - Isovolumic relaxation time (left ventricle)

LA - Left Atrial diameter

LA Enlargement - Voltage criterion for left atrial enlargement

LAE - Voltage criterion for left atrial enlargement

LDR – Long Distance Running

LVED - Maximal left ventricular cavity dimension in end-diastole

LVES - Maximal left ventricular cavity dimension in end-systole

LV - Left Ventricle

LVEDP - Left ventricular end diastolic pressure

LVH - Left Ventricular Hypertrophy

LVM - Left ventricular mass

LVWT - Left Ventricular Wall Thickness in end-diastole

MBA – Male Black Athlete

mLVWT - Maximal left ventricular wall thickness in end diastole

MWA - Male White Athlete

PASP - Pulmonary artery systolic pressure

PTWd - Left ventricular posterior wall thickness in end-diastole

RA Enlargement - voltage criteria for right atrial enlargement

SAM - Systolic anterior motion of the anterior mitral valve leaflet

S' - Systolic annular peak velocity (lateral)

SBP – Systolic Blood Pressure

STE - ST segment Elevation.

T-wave Inv - Distribution of T-wave inversions

UK - United Kingdom

US - United States of America

WA - White Athlete

Chapter 1 – Introduction and Literature Review

1.1 Introduction

The systematic and regular participation in intense physical activity results in central and peripheral cardiovascular adaptation to facilitate the generation of the large and sustained increases in cardiac output to enhance the extraction of oxygen in exercising muscles for aerobic glycolysis. Collectively, these physiological cardiac adaptations have been termed “the athletes heart”.[1] Specifically, both electrical and structural physiological cardiac remodelling occurs, which characteristically regresses following cessation of regular training. Most athletes exhibit alterations in both parasympathetic and sympathetic autonomic tone in combination with modest increases in left ventricular mass, which is reflected in increased left ventricular chamber size and wall thickness.

The phenomenon of the athletes heart was first recognised in Norwegian cross country skiers as early as 1899,[2] and since then many thousands of athletes being have been studied to describe the features of this physiological process. The characterisation of the athletes heart has been facilitated by improvements in both echocardiography[3-7] and electrocardiography[8-11]allowing a detailed description of the cardiac adaptation to physical training to gradually emerge. The majority of these studies have been cross sectional in design and focused on male Caucasian athletes aged 18-35 years. The data has described the magnitude of cardiac enlargement, and identified determinants of cardiac size amongst this population. These have subsequently been used to develop algorithms to allow the differentiation between physiological cardiac adaptation

and cardiomyopathy. Clearly distinction is crucial as world-wide, cardiomyopathies are the leading cause of exercise related sudden cardiac death amongst young athletes (Table 1.1). This includes both hypertrophic cardiomyopathy (HCM), the leading cause of exercise related sudden cardiac death amongst young athletes in the United States,[12] and arrhythmogenic right ventricular cardiomyopathy (ARVC), the commonest cause of exercise related sudden cardiac death in the Vento region of Italy.[13]

With the aim of reducing the incidence of exercise related sudden cardiac death in young athletes, pre participation cardiac screening using both resting 12-lead ECG and 2-D trans-thoracic echocardiography is becoming increasingly widespread throughout the sporting community. Pre-participation cardiac screening has been endorsed by international sporting organisations, such as the International Olympic Committee (IOC),[14] the Federation Internationale de Football Association (FIFA),[15] and by Cardiac societies, including the European Society of Cardiology (ESC).[16,17] Vital to this process, is a clear and accurate understanding of the physiological athletes heart to enable the correct identification of potentially lethal cardiac conditions and prevent an erroneous diagnosis in a healthy individual.

Table 1.1 Causes of sudden cardiac death amongst young athletes aged under 25 in the United States between 1986 and 2007 – Adapted from Maron et al[12]

Diagnosis at Post Mortem	Frequency
Hypertrophic cardiomyopathy	36%
Coronary artery anomalies	17%
Myocarditis	5.9%
Arrhythmogenic right ventricular cardiomyopathy	4.3%
Ion channelopathies (long QT and Brugada syndromes)	3.6%
Mitral valve prolapse	3.4%
Myocardial Bridging	3.3%
Premature coronary artery disease	3.3%
Aortic stenosis	2.4%
Marfan's syndrome	2.7%
Idiopathic dilated cardiomyopathy	2.0%
Wolff-Parkinson-White syndrome	1.6%
Others*	4.9%

* Other causes of death include: Congential heart disease (0.9%), Myocardial infarction (0.9%), Kawasaki Disease (0.7%), Sickle cell trait (0.7%), sarcoidosis (0.6%), stroke (0.4%), cardiac tumour (0.1%), conduction system disease (0.3%), and miscellaneous (not specified) (0.3%).

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screening has been endorsed by international sporting organisations, such as the International Olympic Committee (IOC),[14] the Federation Internationale de Football Association (FIFA),[15] and the by Cardiac societies, including the European Society of Cardiology (ESC).[16,17] Vital to this process, is a clear and accurate understanding of the physiological athletes heart to enable the correct identification of potentially lethal cardiac conditions and prevent an erroneous diagnosis in a healthy individual.

Recent data has suggested that the ethnicity of an athlete is an important determinant of the appearances of both ECG[18] and echocardiogram[19] when taken during a standard pre-participation screen. In particular, male athletes of African/Afro-Caribbean origin occasionally demonstrate physiological ECG and echocardiographic abnormalities that may overlap with the appearances observed in conditions such as HCM and ARVC. Specifically these include repolarisation anomalies in the 12-lead ECG, such as T wave inversions and convex ST segment elevation in the anterior pre-cordial leads, and left ventricular hypertrophy observed on trans-thoracic echocardiography. These studies have however been limited to male athletes who participate in a small number of sports. There is no data available in the literature on female black athletes, and no longitudinal data that describes the significance of these cardiac appearances over time. Given that there has been a dramatic increase in the numbers of black athletes competing in international sporting events and therefore undergoing pre-participation cardiac screening, further data on both female and male black athletes is needed to ensure the accurate interpretation of the 12-lead ECG and echocardiogram in this burgeoning population.

The following sections will summarise data describing the echocardiographic and electrocardiographic characteristics of the athlete's heart, and the current understanding with respect to the impact of demographic factors, including ethnicity and gender, on these appearances. The impact of these physiological changes on pre-participation screening for cardiac causes of sudden cardiac death during sport will then be discussed.

1.2 – The Echocardiographic appearance of the Athletes Heart

During intense sporting activity, the cardiac output may be required to rise from 5l/min at rest, to over 40l/min at peak exertion.[20,21] To enable this augmentation of cardiac output, the heart undergoes both structural and functional modification. Structurally, changes include an increase in both ventricular[5] and atrial size,[22] along with functional enhancement of myocardial relaxation and corresponding indices of diastolic function.[23]

There have been a large number of studies that have utilised trans-thoracic echocardiography to describe the characteristics of physiological cardiac adaptation to exercise. The bulk this data has focused on the structural and functional properties of the left ventricle at rest and have been conducted predominately in Caucasian male subjects, aged over 20 years old. The data derived has been used to develop algorithms that aim to facilitate the differentiation between physiological cardiac adaptation and pathological causes of sudden cardiac death during sport. Given the availability and ease of use, trans-thoracic echocardiography is often used as a first line investigation if

an abnormality is detected in either the clinical history, examination or the 12-lead ECG.

The following section describes the normal appearance of the athletes' heart as observed in routine trans-thoracic echocardiography as well as the impact of demographic factors on the cardiac dimensions observed.

1.2.1 The Left Ventricle

In response to systematic training, the left ventricle undergoes physiological enlargement and increases in mass, when compared to sedentary individuals. This is reflected in an increase in maximal left ventricular wall thickness (LVWT) [4-6] and left ventricular internal diastolic cavity diameter (LVED).[5,7,24]

Measures of left ventricular mass (LVM) utilising traditional M-mode and 2-D echocardiography have demonstrated that athletes consistently develop relative left ventricular hypertrophy when compared to sedentary controls.[4,6,25] Small increases in left ventricular wall thickness and left ventricular cavity can result in a large (>45%) increase in left ventricular mass. These differences are maintained when values are corrected for body mass, surface area and height.

The calculation of LV mass using 2-D measures of left ventricular wall thickness and cavity size makes several assumptions, which introduce inherent inaccuracies into results. Error in the measure of LV wall thickness is magnified within the equation as a cubed function is used to calculate the mass value,. Hence small intra- and inter- observer variability can produce a large variation in

calculated mass. In addition probe positioning bias (Figure 1.1) account for the poor correlation between 2-D echocardiography and the current gold standard technique – cardiac magnetic resonance scanning.[26,27] It is for this reason, that absolute measures of left ventricular wall thickness and cavity size are used routinely in clinical practice to establish the degree of left ventricular hypertrophy in athletes, rather than derived cardiac mass.

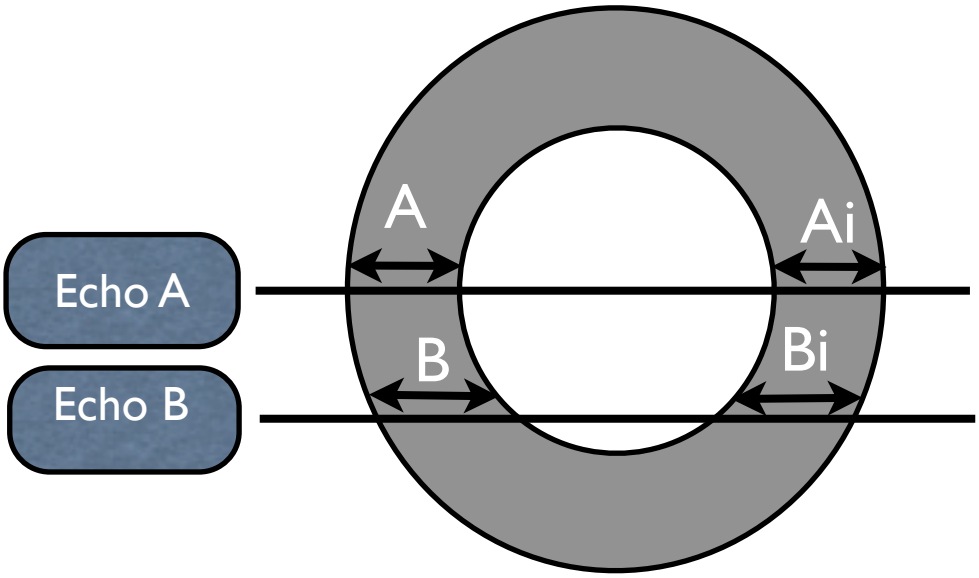

Figure 1.1 - Probe positioning Bias: The probe in position A is aligned to measure the LVWT across the LV axis. In contrast, the probe in position B, only a small distance away, measures a greater value, due to it mal-aligned orientation. ie B> A and Bi> Ai.

1.2.2 Upper Limit of Left Ventricular Wall Thickness in Athletes

A large amount of data has been published on the quantification and description of the physiological left ventricular hypertrophic response to exercise using maximal left ventricular wall thickness (LVWT) as a surrogate for left ventricular mass. These have been used to establish upper limits of left ventricular hypertrophy in male and female athletes to facilitate the differentiation between athletes heart and hypertrophic cardiomyopathy (HCM).

An early meta-analysis of 59 M-mode studies involving almost 1500 highly trained male Caucasian athletes demonstrated a 15-20% increase in left ventricular septal and posterior wall thickness respectively, when compared to sedentary control subjects. However, in terms of absolute values, the mean LVWT in athletes was between 10-11mm and fell within the range accepted for sedentary individuals, outside of that seen in pathological hypertrophic disease states.[5]

More recent two-dimensional echocardiographic studies in large cohorts of highly trained athletes have indicated that the vast majority of athletes have a maximal LVWT of <12mm, which is within the established normal limits for the general population. However, a small minority of male athletes exhibit measures of LVWT that may overlap with that seen in morphologically mild HCM. In an Italian study of 947 male Caucasian Olympic athletes, 1.7% of athletes had a wall thickness exceeding 12mm.[4] Similarly, in a British study of 3500 highly trained Caucasian male athletes, 1.5% of athletes had a maximal LVWT of >12mm (Figure 1.2).[28] The maximal LVWT in both studies was 16mm. therefore it would be reasonable to infer that a a LVWT > 16mm may be representative of pathological LVH, although there are isolated reports of a maximal left ventricular wall thickness of up to 19mm in some endurance athletes. [29,30]

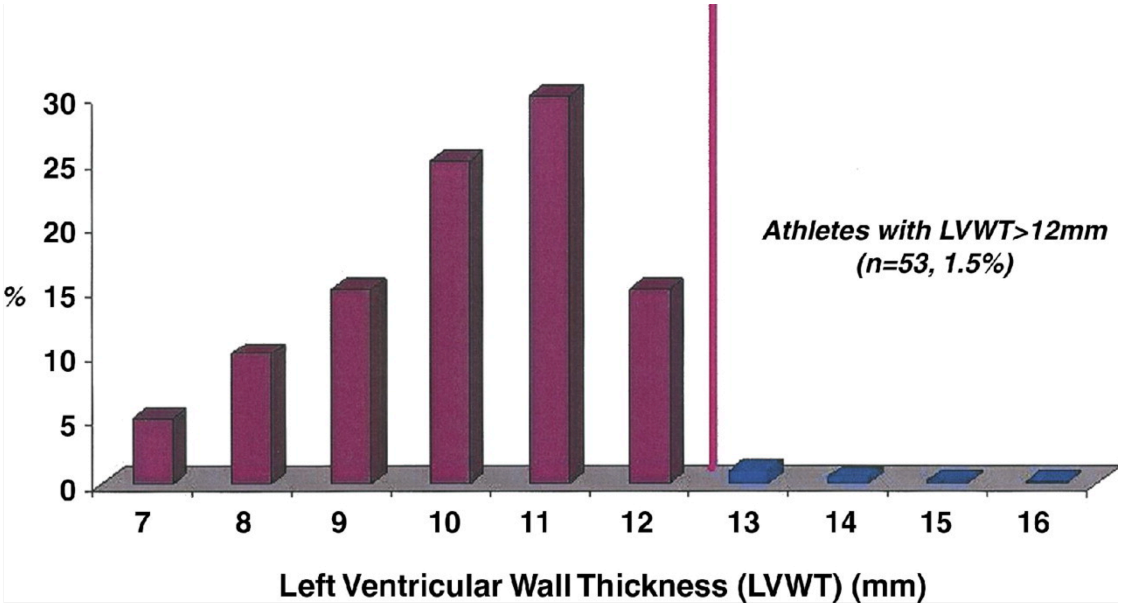

Figure 1.2 Distribution of left ventricular wall thickness in 3,500 highly trained athletes demonstrating that 1.7% athletes exhibit a maximal left ventricular wall thickness of > 12mm. Reproduced from Basavarajaiah et al with permission from the American College of Physicians[28]. Copyright 2008.

With respect to female athletes, less data is available. In one of the few studies pertaining specifically to women that examined the echocardiogram of 600 Italian female Olympic athletes, the maximal LVWT recorded was 12mm.[31] Similarly, a meta analysis of the echocardiographic appearances of 890 female athletes reported an upper limit for maximal left ventricular wall thickness cardiac of 12mm.[32] Unlike male athletes, there is currently no data in the literature reporting physiological left ventricular hypertrophy (LVH) in women which overlaps with that seen in morphologically mild HCM (i.e. of 13mm or greater). Therefore, according to current data, describing exclusively Caucasian athletes, a maximal LVWT of greater than 12mm in any female athlete should be considered pathological hypertrophy.

The majority of studies evaluating the echocardiographic features of athletes have focused on subjects aged 18-35 years old. There is far less data on those adolescent athletes aged <18 years of age, in whom pre-participation screening may have the greatest impact. The largest published study compared over 720 adolescent athletes with 250 age matched sedentary controls. The investigators demonstrated that athletes had a 13% relative increase in maximal left ventricular wall thickness compared to controls. In terms of absolute values, only 4% of athletes exhibited a maximal LV wall thickness of greater than 12mm, with the upper limit of physiological LVH being reported as 14mm in this population.[6](Figure 1.3).

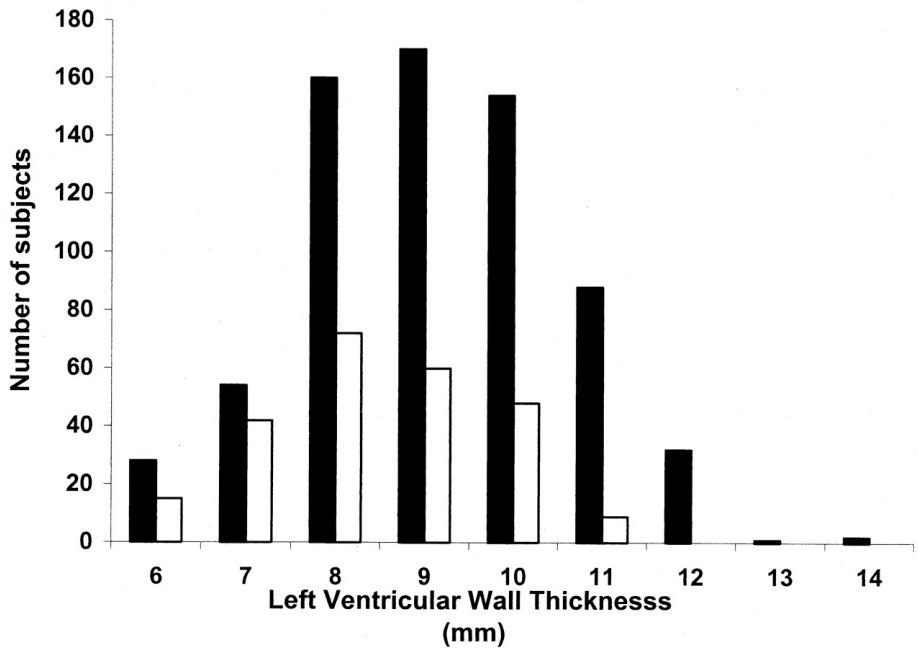

Figure 1.3 Distribution of left ventricular wall thickness in 720 elite adolescent athletes (▪) compared to 250 sedentary control subjects matched for age, size and sex (▫). Reproduced from Sharma et al with permission from the American College of Physicians.[6] Copyright 2002.

1.2.3 Left Ventricular Cavity size

The increase in cardiac mass that occurs in response to regular exercise is reflected not only in left ventricular wall thickness, but also in left ventricular end diastolic cavity diameter (LVED). In a meta-analysis of over 1450 athletes, athletes in all sports demonstrated a significantly greater LVED, when compared to sedentary controls.[55]

In terms of absolute values of LVED, in the majority of athletes the dimensions are within normal limits for the general population. In a population of 1300 elite male and female athletes, with a mean age of 24 years, 55% had an LV cavity size of less than 54mm, within the normal limits for the general population. Of the remaining 45%, 14% had a maximal LVED of greater than 60mm. All had normal indices of both diastolic and systolic function. These athletes were predominately male (97%), and had a substantially larger body surface area when compared to athletes without LV cavity dilatation ($2.12m^2$ ±0.20 v.s. $1.82m^2$ ± 0.21 $P<0.001$). No athlete had an LV cavity diameter of greater than 66mm.[33]

With respect to female athletes, published data is sparse. In a population of 600 Italian elite female athletes, the observed mean maximal LV cavity amongst this group was 11% smaller ($P<0.001$) when compared to a similar population of 738 male athletes. In contrast to male athletes, 8% of female athletes (n=47) in this study had a maximal LV cavity size of >54mm (the accepted upper limit of a normal sedentary individual), and only 1% (n=4) had a maximal LV cavity size

of >60mm, compared to 45% of male athletes in the comparison group.[31] Again, the maximal absolute value of LV cavity size was 66mm.

The effect of age on LV cavity size has been addressed in a single study comparing 900 adolescent mixed male and female adolescent athletes to age matched sedentary controls. Overall, athletes demonstrated an 8% relative increase in maximal LV cavity size. With respect to absolute values, 18% exhibited a maximal LV cavity size of >54mm, with the upper limit of values being 60mm.[34]

1.2.4 Determinants of Left Ventricular Hypertrophy in Athletes

In addition to age and gender, as described above, there are additional factors which affect the magnitude of physiological LVH in athletes. These include body size, the type of sporting discipline in which the athlete participates in, and the ethnicity of the athlete.

The sporting discipline in which an athlete participates is an important determinant of the magnitude of observed left ventricular hypertrophy. In particular, athletes competing in endurance sport with a high isometric and isotonic component such as rowing, canoeing , swimming, cycling and ultra-endurance running exhibit the greatest increase in maximal left ventricular wall thickness. Amongst 947 Italian athletes, all athletes with LVH (n=15;1.7%) participated in rowing, canoeing or cycling.[4] Amongst over 3000 British athletes, LVH was also observed in athletes participating in swimming, professional football, rugby and tennis.[28] Importantly, in contrast to the widely held

misconception, purely isometric sports such as weight lifting or wrestling rarely exhibit a maximal left ventricular wall thickness of greater than 12mm.[5] Within any sporting discipline, the size of the athlete is an important determinant of measurement; a body surface of greater than 2.0m^2 increases the probability of identification of echocardiographic LVH.

More recently, the effect of an athlete's ethnicity upon the magnitude of left ventricular wall thickness has been recognised. A number of studies have been published suggesting that Afro-Caribbean/African (black) male athletes exhibit a significantly greater magnitude of left ventricular hypertrophy when compared to white male athletes of similar size and age who participate in identical sports. The first to suggest this was Lewis et al, who conducted 2-D trans-thoracic echocardiography on 265 collegiate athletes, participating predominately in American Football (48%). They reported that 11% of the black athletes they studied had a maximal LVWT of > 13mm, within the range seen in morphologically mild HCM[35]. This has been followed with data from Basavarajaiah et al who compared 300 highly trained black athletes with a population of 300 highly trained white athletes, of similar size, age and participating in a similar range of ball, racquet and endurance sports, as well as a group of 150 sedentary control subjects. They reported that 18% of black athletes have a maximal LVWT of greater than 13mm, compared with only 4% white athletes, and none of the control subjects ($P<0.001$). In addition, 3% of the black athletes demonstrated a maximal LVWT of >15mm, compared with none of the white athletes (Figure 1.4)[19]. A further study by Magaleski et al, on 1290 American football players, reported trans-thoracic echocardiographic data

limited to 205 of their subjects. Within their study population, 4% had a maximal LVWT of >13mm[18].

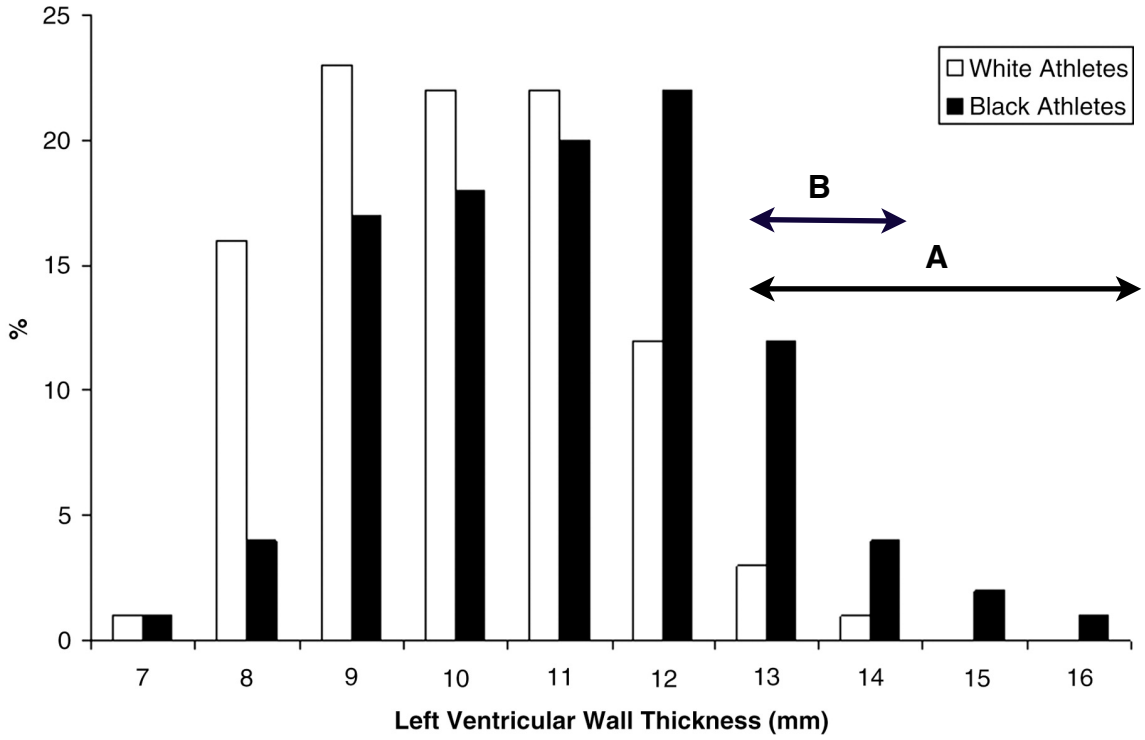

Figure 1.4 Distribution of left ventricular wall thickness in 300 highly trained black male athletes and 300 white male athletes of similar age, size and sporting calibre demonstrating that a significantly higher proportion of black athletes exhibit a wall thickness >12 mm compared with white athletes (8% (line A) vs. 3% (line B), P<0.001). Reproduced from Basavarajaiah et al with permission from the American College of Physicians[19]. Copyright 2008.

In summary, a maximal left ventricular wall thickness of greater than 13mm may be present in 4-18% of black athletes, when compared to 1.8-4% of similar caucasian individuals.. However, these studies are confined to male athletes, all of whom were over 20 years of age There is currently no echocardiographic data evaluating any ethnic differences with respect to female athletes or those athletes less than 20 years of age.

1.2.5 The Right Ventricle

The geometrical structure of the right ventricle makes imaging using trans-thoracic echocardiography technically challenging, with a high intra- and inter-observer variability on measures of RV cavity size. Early echocardiographic studies examined both male[36] and female[37] athletes, who compete in a number of endurance events. These demonstrated that, in general, athletes have a greater transverse right ventricular diameter when compared to sedentary controls. A more comprehensive assessment of echocardiographic right ventricular morphology in a cohort of 650 endurance and strength athletes has recently published data. Amongst endurance athletes, there was a significant increase in transverse right heart diameters compared to both strength athletes and controls. In addition, significant increases in right ventricular outflow tract diameter and right atrial area were also observed[38].

With respect to markers of right ventricular function amongst the 650 individuals studied, there were no significant differences observed between the athlete cohorts and sedentary controls. Amongst endurance athletes however, a wider range of tricuspid regurgitant velocities, pulmonary artery systolic pressures (PASP) and mean pulmonary artery pressures were observed. This did not reflect an increase in pulmonary vascular resistance, which was normal in all subjects. The authors suggested an upper physiological limit of 40mmHg for estimated PASP amongst endurance trained athletes, reflecting the physiological right ventricular chamber enlargement and increase in stroke volume.[38]

The right ventricle has also been studied in detail with cardiac magnetic resonance scanning, which offers a significant improvement over 2-D trans-thoracic echocardiography in terms of definition of the free wall and trabecular structures. An MRI study conducted on 27 male endurance athletes suggested that RV remodeling in response to exercise mirrors that seen in the LV, with an increase in mass, end-diastolic dimensions, and stroke volume. Importantly, the ratio of RV to LV size was maintained – leading the authors to conclude that the athletes' heart syndrome results in balanced remodeling of both ventricles.[39] This is supported by the echocardiographic data and should be considered when assessing athletes, particularly those participating in endurance events, during pre-participation screening.

1.2.6 The Atria

Cardiac remodeling in response to exercise is not confined to the ventricular cavities. In order to facilitate the increase in stroke volume during intense physical activity, the left atrium is required to accommodate an increase in blood volume. Correspondingly, left atrial dilatation is a common finding amongst athletes. This is usually in proportion with any left ventricular dilatation. In a study of 1777 elite Italian athletes, <2% had a maximal LA diameter of greater than 45mm (Figure 1.5). The authors concluded that the upper limit of physiological LA dilatation in this adult population was 50mm.[22] It was associated with participation in dynamic endurance sports such as cycling or rowing, both of which involve prolonged activity of large muscle groups – leading to significant increases in cardiac pre-load [40].

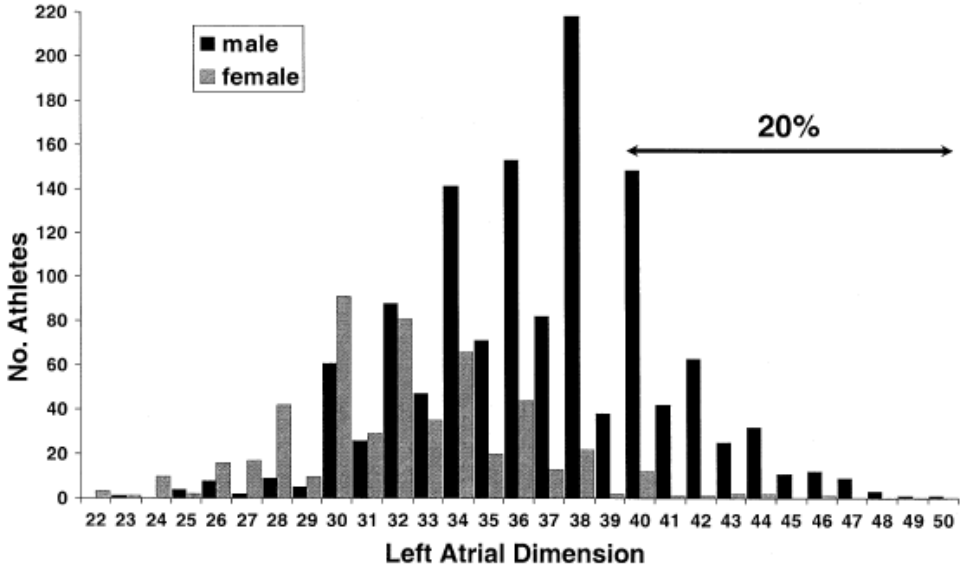

Figure 1.5 Distribution of transverse left atrial dimensions in 1777 highly trained athletes. Data are shown seperately for female (grey bars) and male (black bars) athletes. Twenty percent had an enlarged left atrium (range 40-50mm) including 2% with a left atrial dimension of >45mm. Reproduced by permission of the American College of Cardiology - Copyright 2005.

In contrast, amongst 1000 adolescent elite athletes, the upper limit of LA diameter was 45mm.[41] This may be an indication of the consequences of longer term participation in dynamic endurance sports, with older athletes demonstrating greater left atrial diameters. Importantly, left atrial dilation was again associated with LV cavity diameter. The presence of a dilated left atrium with a normal LV cavity size, and left ventricular hypertrophy, should raise the suggestion of an increase in LV filling pressures, and a potential pathological explanation for this – such as hypertrophic cardiomyopathy – should be sought.[42]

1.3 – The Electrocardiogram in the Athlete

In addition to the structural changes described above, electrical and functional remodelling occurs in response to regular participation in physical activity, reflected in the appearance of the 12-lead surface ECG.[8] In particular, alterations in parasympathetic and sympathetic tone are induced by training. These are fundamental to the physiological cardiac adaptive process[8] allowing an increase in both the efficiency of cardiac contraction and a sustained cardiac output.

As a consequence of the alterations in autonomic tone, in certain circumstances, the normal appearance of the athletes ECG may mimic that seen in cardiomyopathy, ion channel disease and other structural heart disease. Therefore, the correct interpretation of the 12-lead surface ECG in the athlete is essential and forms a central part of the recommendations for pre-participation screening endorsed by the ESC,[14,17]the IOC,[14] and FIFA.[15]

1.3.1 – Common Findings on the Resting 12-lead ECG (Table 1.2)

Common findings on the resting 12 lead ECG include sinus bradycardia (present in up to 80% of trained athletes),[10] sinus arrhythmia (52%) and 1st degree heart block (5%) (Figure 1.6) These are considered to be secondary to increased vagal tone, although alterations to the intrinsic properties of the SA and AV node have also been described and may contribute.[43]

Table 1.2 – Common Findings in the resting ECG in the Athlete[9]

ECG Finding	Frequency (%)
Sinus Bradycardia	80%
Sinus Arrhythmia	52%
1st Degree AV Block	5%
Incomplete RBBB	29%
LA Enlargement	14%
RA Enlargement	16%
Sokolow-Lyon criteria for LVH	45%
ST-elevation	43%
“Giant” T-waves	22%

Abbreviations

AV= atrio-ventricular node, “Giant” = T wave voltage >0.2mV, LVH = left ventricular hypertrophy, LA Enlargement = Voltage criteria for left atrial enlargement, RA Enlargement = voltage criteria for right atrial enlargement, ST = ST segment elevation.

An increase in QRS complex voltages, particularly across the precordial leads is observed in up to 60% of athletes. This can only in part be attributed to an increase in cardiac size, as there is a poor correlation between the commonly used voltage criteria for cardiac hypertrophy (Sokolow-Lyon, Cornell) and cardiac dimensions observed on trans-thoracic echocardiography. Several other factors affect QRS voltage including the distance between the heart and the chest wall which is influenced by chest wall size, pectoral hypertrophy and the presence or absence of breast tissue.

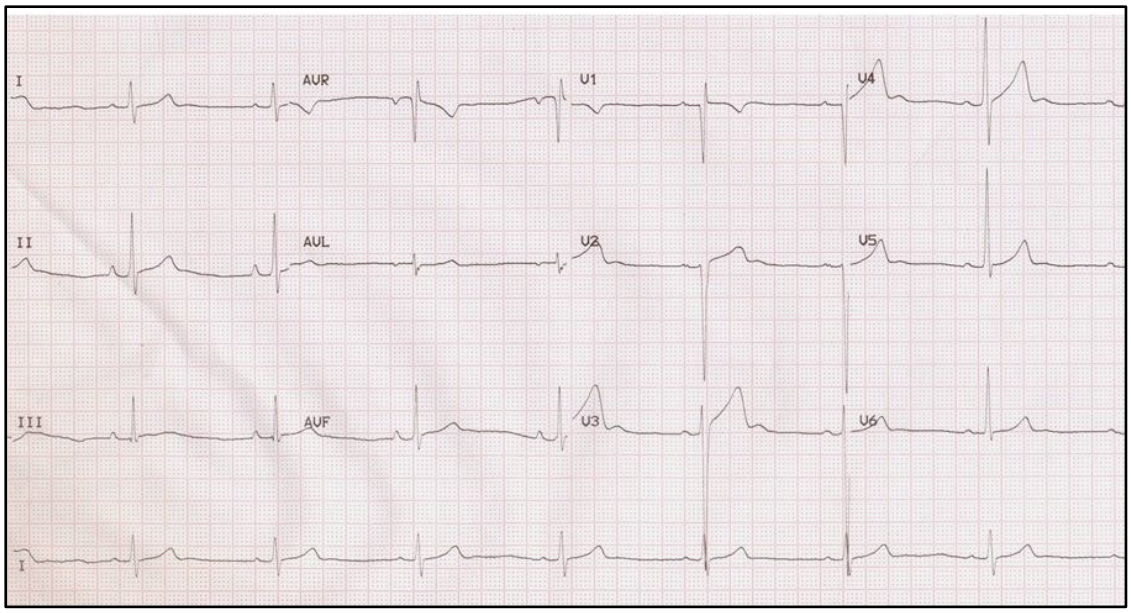

Figure 1.6 A normal Athletes ECG – taken from a young professional cyclist during routine pre-participation screening. His ECG demonstrates sinus bradycardia, voltage criteria for left ventricular hypertrophy, and "giant" (T wave >0.2mV) precordial T-waves.

Other common findings in athletes include the presence of incomplete right bundle branch block (29% of highly trained athletes),[9] and voltage criteria for left and right atrial enlargement, present in 14% and 16% of adolescent athletes respectively.[9](figure 1.6) The sensitivity and specificity of such voltage scores is also poor, with only 0.3% of 347 adult athletes with echocardiographic evidence of left atrial enlargement having positive voltage criteria.[22]

1.3.2 Repolarisation Changes

Amongst athletes, early repolarisation changes are common consist predominately of J point and ST segment elevation, and increased T wave voltages (>0.2mV or "giant" T waves). These changes are present in between 40-50% of individuals,[9] and reflect alterations in autonomic tone affecting the timing sequence between depolarisation and repolarisation. In general, these

are considered benign (Figure 1.6), in the absence of symptoms or any specific family history of sudden cardiac death.

However, it is the presence of other repolarisation changes – in particular T wave inversions and ST segment depression – that may be attributed to athletic adaptation but may overlap with phenotypic manifestations of cardiomyopathy,[44,45] ion channel disorders,[46,47] and anabolic steroid abuse.[48] These are unusual findings in athletes, being present in only 3-4% of Caucasian adolescent[49] and adult athletes[11]. The juvenile ECG pattern consisting of T wave inversions beyond V1 (V1-V3) usually resolves by the age of 16 years old. In general, Caucasian athletes who demonstrate such an ECG appearance should undergo thorough evaluation before the findings should be attributed to physiological adaptation (Figure 1.7)

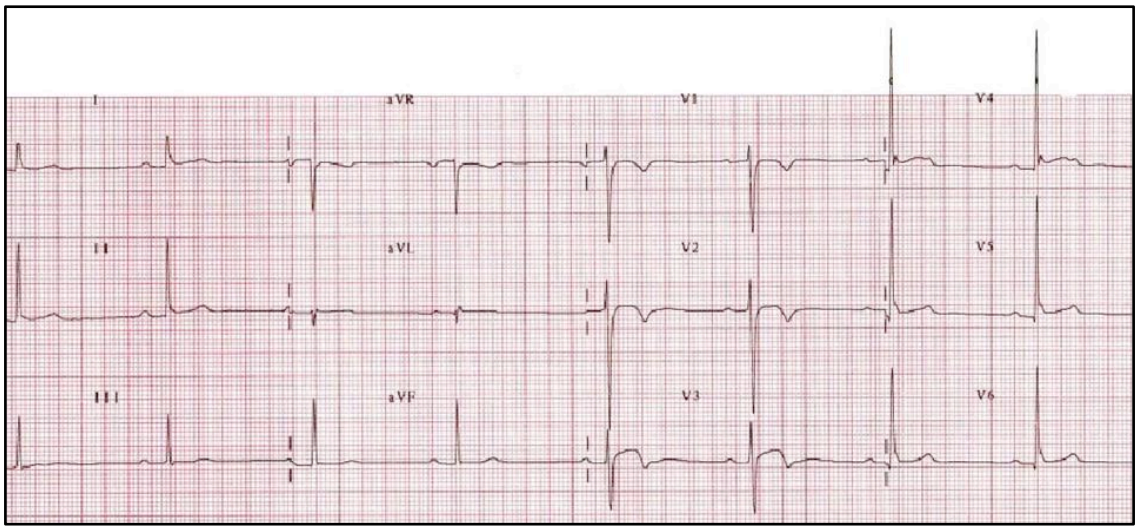

Figure 1.7 – 12-lead ECG taken from a 15-year old Caucasian male junior elite tennis player demonstrating T-wave inversions in the anterior leads (V1-V3), consistent with the juvenile ECG pattern. His trans-thoracic echocardiogram was entirely normal.

The appearance of the normal resting 12 lead ECG – including the presence of repolarisation anomalies (i.e. T wave inversions), voltage criteria for ventricular hypertrophy and left or right atrial enlargement - is affected by a number of demographic factors.

1.3.3 Demographic factors affecting the appearance of the Athletes ECG

In a similar pattern to the data relating to trans-thoracic echocardiography, the majority of data from which the appearance of a normal athletes ECG has been determined, relates to adult Caucasian male subjects. However, the effect of a variety of demographic factors upon the range of normal ECG patterns observed has been recognised. These are mentioned briefly above, and include the athletes' ethnicity, sex, age, and body size.

1.3.3.1 Ethnicity

Historically, racial differences in the appearance of the 12-lead ECG have been recognised, with a number of observational papers in the 1950's that suggest that J-point and ST-segment elevation may be part of the normal ECG in young black men,[50-52]. They also describe bizarre repolarisation patterns that may simulate myocardial infarction or phenotypic manifestations of both hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy[52] (a condition yet to be described at the time these papers were written) (Figure 1.8). This concept has recently been revisited by a number of papers examining the ECG in a range of black male athletes.

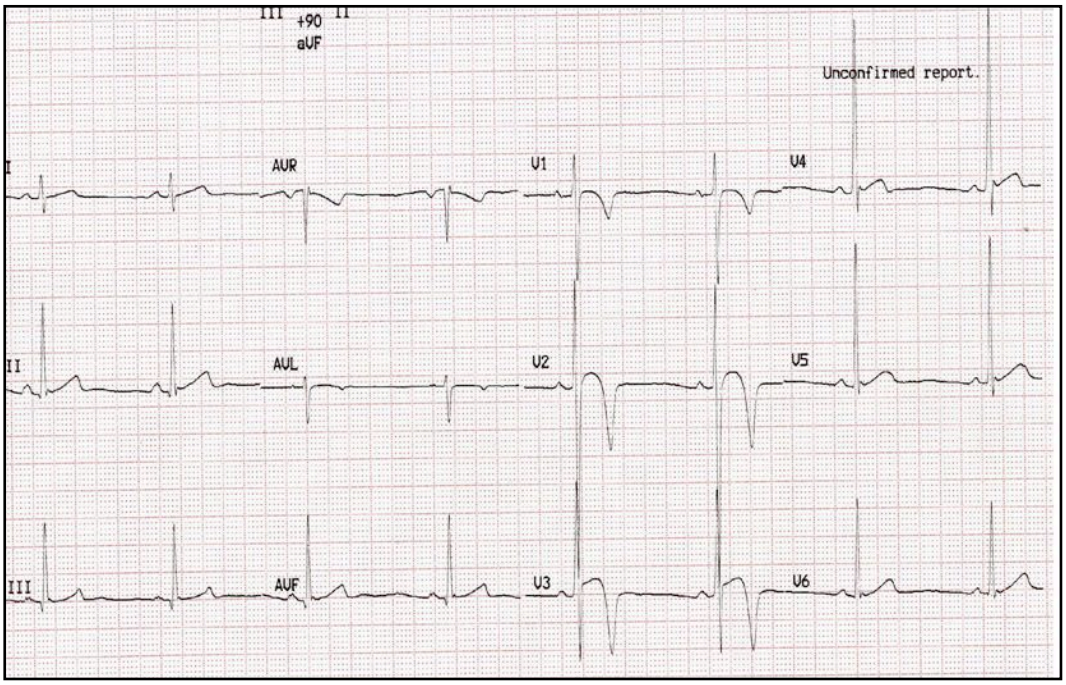

Figure 1.8 - 12-lead ECG taken from a male African endurance athlete, a medallist at the 2008 Bejing Olympics. Note the deep T-wave inversions and convex ST segment elevation in the anterior pre-cordial leads (V1-V3). He subsequently underwent further evaluation which did not reveal any underlying cardiac abnormalities.

The first of these examined the ECG appearance in 289 male American footballers. They noted that 39 players demonstrated significant ST-T wave changes that mimicked ischaemia, and 22 of these (representing 7.6% of the total athletes studied) were black. The authors were unable to subsequently assess athletes with echocardiography due to the circumstances in which the study was conducted, but concluded that these represented normal ethnic variation.[53] This was followed by a larger and more comprehensive study, again in male American football players. From a population of 1282 athletes, 835 were described as black. They reported ST segment and/or T wave abnormalities occurring in 20.5% of black individuals, compared to 9.4% of white athletes ($P<0.001$). They noted no differences in the frequency of voltage criteria for left or right ventricular hypertrophy. The athletes with an ECG suggestive of cardiomyopathy or ischaemia underwent trans-thoracic echocardiography, but no athlete was subsequently diagnosed with a cardiac condition.[54] More recently, a further study of 1,959 male athletes, again American footballers, of which 1,321 (67%) were black, reported that 5.8% of black players had an ECG appearance that was deemed “markedly abnormal” by the investigators, when compared to only 1.8% of similar white players. The term “markedly abnormal” encompassed T wave inversions, left or right axis deviation, the presence of pathological Q waves, and significant inter-ventricular conduction delay. Only 33 of the 88 athletes with abnormal ECGs underwent subsequent echocardiographic examination, the numbers studied being insufficient to draw any correlations between ECG and echocardiographic appearance.[18] The authors of all these studies concluded that that in the majority of cases, these changes are benign and represent normal ethnic variation.

All these studies are limited in that they report results in athletes who participate in only a single sport – American football, which has little relevance to the wider sporting community in countries other than the US. All athletes are male, aged over 20, and have an average height of 1.84±0.07 m and weight of 103±18 kg. It is sport in which females do not participate at all in any numbers. In all these studies, one should also consider the use of illicit performance enhancing drugs (in particular, the use of anabolic steroids), whose use in the National Football Leagues (NFL) over the period in time in which the earlier studies were conducted, was widespread.[55]

The only data regarding the appearance of the athletes ECG in black athletes available upon sports other than American football, is from an echocardiographic study of 300 black and 300 white male athletes from Basavarajaiah et al.[19]They report that amongst athletes with left ventricular hypertrophy (i.e. a maximal LVWT of >12mm), black athletes had a higher prevalence of voltage criteria for left ventricular hypertrophy (37 (68%) vs. 5 (40%); $p<0.001$), ST segment elevation (46 (85%) vs. 7 (62%); $p<0.001$), and T wave inversions (7 (12%) vs. none (0%); $p<0.001$). The distribution of T wave inversions observed was confined to leads V1-V4 and was present in 4 of the 9 athletes that demonstrated a maximal LVWT of ≥15mm. T-wave inversions were not present in any white athlete with LVH. The determinants of T wave inversions were not studied in depth in this paper, but the athletes participated in a wide variety of sporting disciplines (including boxing, basketball, track athletics, and football) and were of similar size to controls and black athletes without T wave inversions. However, again this was confined to male athletes, over the age of 18.

With respect to female black athletes, there is currently no specific data available in the literature.

1.3.3.2 Gender

In general, females have a lower lean body mass, and tend to exhibit smaller quantitative electrocardiographic changes when compared to males. Males exhibit higher voltages and longer complex/interval durations e.g. PR interval, QRS duration and QT interval.[17]

Overall, there is limited data available with respect to the female athletes ECG across the demographic spectrum, as the majority of studies assessing cardiac adaptation in response to exercise have been conducted predominantly in Caucasian male subjects.

There are few specific studies in the literature that examine the appearance of the ECG in the female athlete. Through cohort studies that examine both male and female athletes (in smaller numbers), one can determine that Caucasian female athletes seem to exhibit a lower prevalence of ECG abnormalities when compared to similar male subjects. The first of these to report was from a Norweigen cohort of 1299 physical education students, of which 617 (47%) were Female.[56] Overall, male athletes had lower heart rates, with increased voltages and a higher prevalence of voltage criteria for LVH when compared to similar females. No distinction was attempted amongst this group between normal and abnormal, other than for conduction disease (e.g. the presence of

an accessory pathway), where there were no specific differences noted between the sexes. Pelliccia et al reported ECG findings in 1005 highly trained Italian athletes, 25% of which were female.[11] They found that a significantly lower proportion of female athletes had “distinctly abnormal ECG’s”, 8% vs. 17% ($p<0.001$). The vast majority of female athletes studied had entirely normal ECGs (78% vs. 55%; $P<0.001$). This has been followed by two large studies conducted in Italy, reporting results based upon an unselected group of individuals who attended one of the 19 clinics in Italy who conduct the mandatory annual pre-participation screening required to compete in any sporting activity. Pelliccia at al reported data on a population of 32,652 individuals, 6602 (20%) of which were female. Of these, 9.6% exhibited an ECG deemed “markedly abnormal” by the investigators, compared to 12.4% of males ($P<0.001$).[57] Sofi et al reports data on 30,065 individuals, 6495 (21%) of whom were female.[58] In total, a lower proportion of athletes (6%) were deemed to have a “markedly abnormal ECG”, based on the same criteria as Pelliccia. With respect to gender differences, again, a significantly lower proportion of women had abnormal ECG’s when compared to men (Women 3.7% vs. Men 6.7%; $p<0.001$). However, when considers the individual abnormalities, a similar percentage of men and women demonstrated significant ST-T wave alterations (0.5% vs. 0.5%;$p=0.9$), which included T-wave inversions.

With respect to female adolescent athletes (i.e. those under 18 years old), only a few data is available. In a study of 1000 adolescent predominantly Caucasian athletes, of which 270 (23%) were female, voltage criteria for LVH, right and left atrial enlargement and partial right bundle branch block, were more common in male athletes than female athletes, with only 5% of female athletes

demonstrating Solokow-lyon voltage criteria compared to 60% of male athletes ($p<0.001$).[9] Papadakis et al, in a similar population of 1710 largely Caucasian adolescent athletes[49] observed that only 1 of the 296 female athletes studied (0.3%) demonstrated significant T wave inversions, compared to 66 (4.7%) of male athletes studied ($p<0.001$).

All the studies above have been conducted in predominately Caucasian athletes with no specific data available with respect to cardiac adaptation in black female athletes of any age.

1.4 Differentiation between Physiology and Pathology

The data described in the above sections describes the impact of physical conditioning on the appearance of both the echocardiogram and ECG in the athlete. The ability of a physician to accurately interpret these investigations is the mainstay of an effective pre-participation cardiac screening program. The clear differentiation between physiology and pathology is essential to allow appropriate intervention to minimise the risk of sudden cardiac death in an individual with a cardiac disorder, and conversely prevent an erroneous diagnosis in an otherwise healthy young person.

Hypertrophic cardiomyopathy (HCM) and arrythmogenic right ventricular cardiomyopathy (ARVC) are the commonest causes of sudden cardiac death in the United States[59] and Italy[13] respectively. Therefore, the identification of features of either condition, notably left ventricular hypertrophy on echocardiography and/or electrocardiographic repolarisation anomalies, in an

individual at cardiac screening requires further thorough evaluation. Both findings can be the consequence of physiological adaptation, but careful assessment is necessary before they are attributed to this benign process. The following sections will describe current methods that are employed in the differentiation between athletic adaptation and cardiomyopathy as seen on the 12-lead ECG and trans-thoracic echocardiogram.

1.4.1 Left Ventricular Hypertrophy

As detailed above, the finding of left ventricular hypertrophy (a maximal left ventricular wall thickness of 13-16mm) in an athlete may occur in up to 4% of caucasian athletes and up to 18% of black athletes. This measure overlaps with vales observed in 10-15% of patients with morphologically mild HCM[28]. The majority of such findings can be attributed to physiological conditioning, however careful examination of the echocardiographic and clinical parameters should be undertaken to exclude pathological forms of myocardial hypertrophy.

The vast majority of individuals with HCM find themselves unable to excel in sport due in part to the limitations in cardiac function imposed by this condition. However, there is marked morphological and functional heterogeneity, and outstanding athletic achievement is possible in some individuals.

The differentiation between pathological and physiological hypertrophy is usually clear, however may challenge even the most able cardiologist. The approach taken should be systematic, with a detailed history (including a comprehensive family tree and demographic assessment), physical

examination, 12-lead ECG and trans-thoracic echocardiography. If the diagnosis is unclear, then further imaging with cardiac magnetic resonance scanning, cardiopulmonary exercise testing , and screening for causal genetic mutations may be required in equivocal cases.

1.4.1.2 Impact of athlete demographics on the diagnosis of HCM

When assessing an athlete with mild LVH, careful consideration of an athlete's race and sex should be undertaken whilst establishing the diagnosis. The impact of both these demographic variables on the process of physiological adaptation has been described in section 1.2.

Precise details on the relative incidence of HCM in different ethnic groups is not available in the current literature, but expert consensus does not currently recognise a racial predilection.[42,60] HCM has an estimated prevalence of 1 in 500 amongst western populations, based upon a number of epidemiological studies[61 62]. In general, these report data on mainly caucasian subjects, with only a small proportion of the study population comprising Afro-Caribbean individuals.. Amongst a large cohort of patients diagnosed with HCM in one US registry, Afro-Caribbean patients represent only 8% of the cohort. This data however is likely to be affected by the various socio-economic factors that impact the availability of healthcare in the US[63].

Similarly, the majority of genetic mutations identified as causing the HCM phenotype are inherited in an autosomal dominant fashion.[42] There does not appear to be an overall gender preference, and both males and females are

affected by the condition in equal numbers. Therefore, the diagnosis of HCM in a black athlete, male or female, is at present established on guidelines based on predominately caucasian subjects. Given the data presented in section 1.2, care should be taken to examine the echocardiogram and 12-lead ECG for features of HCM beyond absolute measures of left ventricular wall thickness.

1.4.1.3 Role of Trans-thoracic Echocardiography in the diagnosis of HCM

Trans-thoracic echocardiography is an essential tool in the differentiation between pathological and physiological LVH in the highly trained athlete. It allows rapid and non invasive assessment of the myocardial structure and function, with information on the magnitude and distribution of left ventricular hypertrophy, associated left ventricular outflow obstruction, and indices of systolic and diastolic function. The presence of, or alterations in, these important structural and functional measures can be essential in establishing the diagnosis of a cardiomyopathy in an athlete.

1.4.1.4 Structural Markers of HCM at Echocardiography

The discrimination between pathological and physiological hypertrophy should take into account the full echocardiographic study, rather than a single measure of left ventricular wall thickness in isolation. The upper limit of physiological hypertrophy in athletes is considered to be 16mm, and the data that support's this have been described in section 1.2.2. Therefore, the identification at echocardiography of LVH of greater than 16mm, in any cardiac segment, should

be considered to be pathological and further investigation should be undertaken.

Physiological LVH is homogeneous, symmetrical and athletes rarely exhibit differences of >2mm between adjacent LV myocardial segments. The ratio of inter-ventricular septal wall thickness to the LV posterior wall thickness in end-diastole is <1.5.[64] In contrast, almost any pattern of hypertrophy is possible in HCM, and contiguous portions of left ventricle may vary significantly in the the magnitude of LVH. Of note, 60% of individuals with HCM exhibit asymmetrical septal hypertrophy, with a further 10% demonstrate hypertrophy confined purely to the LV apex.[60]

The left ventricular cavity size often the most useful additional measure. Almost all athletes with physiological LVH have concomitant enlargement of the left ventricular cavity, with only a minority exhibiting normal left ventricular dimensions.[24] HCM is characterised by disparity between the magnitude of LVH and the left ventricular cavity size, with LVH occurring at the expense of left ventricular cavity size. Most individuals with HCM have a small left ventricular cavity (<45mm).[42] A dilated ventricle is a marker of end stage disease; a consequence of progressive myocardial fibrosis, increased LVEDP, and associated with impaired systolic and diastolic function and accompanied by significant functional limitation.

Approximately one quarter of individuals with HCM exhibit basal, dynamic left ventricular outflow tract obstruction at rest[65] and up to 70% develop obstruction with exercise, the majority due to systolic anterior motion (SAM) of the anterior

mitral valve leaflet against the inter-ventricular septum.[66] This phenomenon has been attributed to several factors, including the presence of asymmetrical septal hypertrophy, anteriorly displaced papillary muscles, redundant mitral valve leaflets, a narrow LVOT and hyper-dynamic systolic function. The demonstration of SAM and associated LVOT obstruction at rest or immediately after exercise in an athlete with LVH is considered consistent with the diagnosis of HCM.[65]

1.4.1.5 Functional Markers of HCM at Echocardiography

In an athlete with physiological LVH, conventional indices of diastolic function (mitral valve inflow Doppler and pulmonary vein Doppler measurements) are normal. These individuals have a compliant ventricle that is capable of efficient left ventricular filling to maintain a high stroke volume at approaching maximal heart rate.[67] In contrast, individuals with HCM have an increase in myocardial stiffness as a consequence of myocyte disarray, myocardial fibrosis, and impaired sarcoplasmic calcium kinetics - all resulting in impaired myocardial relaxation. Hence, early passive left ventricular filling is blunted and impaired. This is reflected in a reversal of the E/A ratio, prolongation of the E-deceleration time (>240 msec) or isovolumic relaxation times (>90 msec), and reversed S/D ratio during pulmonary vein Doppler.[68]

More recent studies utilizing colour coded and pulsed tissue Doppler echocardiography have provided more sensitive and specific methods of differentiating physiological LVH from HCM.[69,70] Measurement of myocardial velocity gradients from digitised M-mode colour Doppler reveals that individuals with HCM exhibit impaired myocardial filling during the early rapid filling phase

of diastole and display reduced left ventricular posterior wall myocardial velocity gradients when compared to athletes. In a small study comparing comparing individuals with HCM (n=25) and athletes with physiological LVH (n=21), suggests that a myocardial velocity gradient of <7 s-1 measured in early diastole may be a sensitive and specific marker in differentiating physiological from pathological LVH.[71]

Assessment of longitudinal cardiac function with pulsed tissue Doppler at the level of the mitral valve annulus has shown that individuals with morphologically mild HCM, including those individuals with normal mitral inflow Doppler measurements (E/A), exhibit lower early diastolic velocities (Ea or E') when compared with athletes. An E' of <9m/s suggests pathological LVH, with a sensitivity approaching 90%.[23] In addition, an E/E' ratio may be useful,[70] with an E/E' of >12 being indicative of an increase in left atrial filling pressures - a recognized pathophysiological feature of HCM. However, the majority of trained athletes exhibit an E/E' of <8 as a consequence of the increase in left ventricular compliance and associated low filling pressures. (Table 1.3)

Indices of systolic function are conventionally based on the percentage change in left ventricular volume between systole and diastole. As a consequence of the small left ventricular cavity size and modest changes in the absolute volume of the LV, the percentage change (ejection fraction) in LV volume in patients with HCM may be high. When one considers other, more subtle, indices of systolic function - including pulsed tissue Doppler studies - many individuals with HCM have impaired longitudinal and radial systolic function. In general, the

identification of a peak systolic velocity of <9cm/s at the mitral valve annulus in an athlete with LVH should suggest pathological substrate.[72](Table 1.3)

Table 1.3 Echocardiographic indices used in the differentiation between physiological and pathological left ventricular hypertrophy.

Structural Markers Of HCM	Functional Makers of HCM
Maximal LVWT > 16mm	E/A reversal (ratio <1.0)
Asymmetric Hypertrophy (>2mm)	E Decel >240 msec
Small (<45mm) LV cavity	IVRT >90 msec
SAM ± LVOT gradient at rest	Myocardial Velocity gradient < 7 s-1
Dilated LA	E' (lateral) < 9m/s
	E/E' >12
	Peak S' < 9cm/s

Abbreviations - A = late diastolic mitral valve inflow peak velocity, E = early diastolic mitral valve peak inflow velocity, E Decel = E wave deceleration time, E' = early diastolic annular peak velocity (lateral mitral annulus), E:E`=ratio of peak early diastolic mitral inflow velocity to peak early diastolic mitral annular velocity HCM = hypertrophic cardiomyopathy, IVRT = Isovolumic relaxation time, LVWT = left ventricular wall thickness, LV = left ventricle, LA = left atrium, LVOT = left ventricular outflow tract, SAM = Systolic anterior motion of the mitral valve, S' = systolic annular peak velocity (lateral)

1.4.1.6 Further assessment of LVH in the athlete

The trans thoracic echocardiogram is an essential part of the assessment of an individual in one whom the diagnosis of HCM is suspected. No single

echocardiographic parameter should be taken in isolation to be diagnostic, but should form part of a comprehensive clinical assessment, including the clinical history, examination and 12-lead ECG. The ECG changes that may be present in HCM will be discussed in section 1.4.2.

Despite this, the cause of LVH in the athlete may remain equivocal. There are further, less widely available non-invasive clinical investigations that may prove invaluable to the clinician required to assess an athlete with LVH.

The measure of peak oxygen consumption during an exercise test can be a useful method of differentiating physiological from pathological LVH. Athletes participating in endurance sports have a large peak oxygen consumption. A peak oxygen consumption of > 50ml/kg/min (or 120% of that predicted for age) in an athlete with mild LVH favours physiological adaptation.[73] In contrast, most individuals with HCM have a sub-normal peak oxygen consumption irrespective of the magnitude of LVH and function capacity of the individual. The combination of impaired myocardial relaxation, associated with myocardial fibrosis, a small left ventricular cavity size, exercise related myocardial ischemia, and dynamic left ventricular outflow tract obstruction results in an innate inability to generate the large and sustained increases in stroke volume and cardiac output required in elite sport.

Additional imaging with cardiac magnetic resonance (CMR) imaging can provide valuable data on cardiac structure and function in addition to trans-thoracic echocardiography. With respect to cardiac structure, CMR provides better definition of the cardiac apex and antero-lateral wall, allowing

demonstration of LVH in these segments that may not clearly be seen using trans-thoracic echocardiography (TTE)[74] In particular, the use use of gadolinium enhancement to identify and quantify regional myocardial fibrosis can be very helpful in the differentiation between physiology and pathology. Approximately 50% of individuals with pathological LVH due to HCM exhibit significant myocardial fibrosis[75] which is not seen in athletes with physiological LVH. The identification of fibrosis strongly favours of a pathological form of hypertrophy.

Given the diverse appearances and manifestations of HCM, there is no one isolated investigation that will identify all individuals with HCM. it may be necessary to subject the athlete in question to a period of detraining - usually around 3 months - followed by comprehensive re-assessment. Physiological LVH should regress, whereas pathological hypertrophy should persist, albeit to a lesser extent. This is associated with anxiety as well as potentially jeopardizing fitness and future team selection. It should therefore be only advised if the athlete fully understands the implications involved and cooperates fully, as even a limited training may cloud the ability to make a clear diagnosis.

The differentiation between pathological and physiological LVH may be extremely difficult, particularly in athletes of Afro-Caribbean ancestry, amongst whom little information exists regarding the spectrum of electrocardiographic and echocardiographic appearances in response to physical activity. More data is required to enable clinicians to make an accurate and correct diagnosis, and allow afro-caribbean athletes to continue to excel at sport.

1.4.2 Repolarisation anomalies

The pre-participation screening program advocated by the ESC[16,17] and IOC[14] include a 12-lead ECG as part of the assessment of an athlete. The presence of repolarisation anomalies (including ST segment depression and T-wave inversions in 2 or more contiguous leads) in an ECG is often the trigger for the athlete concerned to undergo further investigation to exclude a cardiomyopathy[44 16,45], ion channel disease[46] or other cause of sudden cardiac death during sport.

Amongst caucasian athletes, such repolarisation anomalies are present in 3-4% of male adult and adolescent athletes. As has been discussed in section 1.3.3, the prevalence of significant T-wave inversions is significantly lower in caucasian female athletes, and considerably higher amongst male black athletes. There is currently no published data available on the ECG appearance in black female athletes. Given their relative rarity, current guidance suggests thorough evaluation of any athlete exhibiting such an ECG appearance in order to exclude occult cardiac disease.

Data on the significance of such ECG anomalies is currently only available relating to male caucasian athletes. In a longitudinal study of 123 adult male athletes with deep T wave inversions, who presented at routine cardiac screening, 39 (32%) had echocardiographic and clinical evidence of cardiac disease. Of the remaining 84 athletes, who had no immediately demonstrable evidence of cardiac disease, 81 were followed up for a mean of 9 years (+/- 7

yrs.; range 1-27). Of these, 5 athletes (6%) subsequently developed a cardiomyopathy, with one death and one aborted cardiac arrest as a consequence of ventricular fibrillation due to ARVC and HCM respectively. The remaining 70 athletes did not develop any pathological cardiac conditions during the period of follow-up. This data suggests that the presence of repolarisation anomalies, such as deep T wave inversions, in a caucasian athlete may represent occult cardiac disease, and as such, the individuals should remain under periodic surveillance.

As has been discussed in section 1.3.3, significantly greater numbers of black male athletes exhibit T wave inversions on the resting 12-lead ECG. These are predominately confined to the anterior precordial leads (Figure 1.8). there is currently no data available with respect to the long term significance of such ECG changes, and whether a proportion of such individuals may harbor a cardiomyopathy.

1.5 Pre-Participation Cardiac Screening of Athletes

The sudden cardiac death of a young athlete during a sporting event is a tragic and thankfully unusual event. Estimates vary with respect to the precise incidence. Data from the United States reports an incidence of 0.5 per 100,000 per year.[59] However, this is retrospective, based on collating mortality data from sporting institutions and media reports and likely therefore to represent an underestimate. Further retrospective data from the database of the NCAA (National Collegiate Athletic Association), reports an incidence of sudden cardiac death of 1 in 43700 participants per year amongst collegiate level

athletes, assessed over a 5 year period.[76] Prospective data from Northern Italy suggests an overall incidence of 2.1 deaths per 100,000 per year.[13] The incidence in the UK is unknown, as no systematic registry of deaths during sporting activity exists.

These events are often highly visible and generate considerable media and public interest. The causes of these deaths are multiple (Table 1.1) and include cardiomyopathies, inherited anomalies of the coronary arteries, and ion channel diseases. With advances in management and treatment of these conditions, once identified sudden death may be preventable. Given this fact, many sporting organisations, including FIFA,[15] the IOC,[14] the LTA (Lawn Tennis Association), and IRB (International Rugby Board) have advocated pre-participation screening for all athletes who are engaged in international competition. They are supported in this by international cardiac societies such as the ESC[17]. However, the diversity and low population prevalence of the conditions that need to be identified means that a large number of athletes need to be screened to identify a small number of individuals who harbour a serious cardiac disorder.

In common with most western countries, the UK does not advocate a compulsory state sponsored pre-participation screening program. The majority of data examining the efficacy of such a system is derived from Italy, where state sponsored pre-participation screening has been written into the statute books since the late 1970s. Pre-participation screening is also advocated in the United States at a collegiate athlete level[77] – but to a lesser extent than in Italy.

Hence, the bulk of data available regarding the efficacy of such screening programs has been derived from these two countries.

1.5.1 Methods of pre-participation screening

The evidence that supports the use of pre-participation screening has been collated in both the US and Italy. However, the two countries have adopted differing approaches to the identification of conditions that may pre-dispose a young individual to sudden cardiac death during intense physical activity.

The American model of pre-participation screening comprises a focused history, assessed by means of a health questionnaire particularly concerned with cardiac symptoms and family history of cardiac disease, and a clinical examination.[77]This approach has a low sensitivity and specificity for the identification of occult cardiac disease which may pre-dispose an individual to sudden cardiac death during sport. 80% of victims during exercise are asymptomatic prior to the lethal event, and the majority of causes are not identifiable on examination alone. This is highlighted by a retrospective analysis of a series of 134 sudden cardiac deaths over a 10 year period in the U.S. 115 had undergone pre-participation screening, with a focused history and clinical examination, with only a single athlete correctly diagnosed at the time of screening.[59]

Current legislation in Italy mandates an annual pre-participation cardiac screen for all athletes that participate in any organised sporting event. This legislation has been in place since 1976, and has resulted in Italian physicians developing

unique experience in the pre-participation screening of athletic individuals. The screening process used involves a focused history, examination and 12-lead ECG. The addition of the ECG to the screening protocol increases both the sensitivity and specificity of the screening process. It facilitates the identification of cardiomyopathies with 95% of individuals with HCM, and 80% of individuals with ARVC, having electrocardiographic abnormalities.[78,79] In addition, the diagnosis of ion-channel disorders and accessory pathways are dependant upon electrocardiography.[79] All are recognised causes of sudden death during sporting activity.[12,59]

Evidence to justify to addition of a 12-lead ECG to a history and examination has come from several prospective large demographic studies examining the efficacy of the Italian programme. With respect to the identification of cardiovascular disease, amongst a population of over 33,000 screened in the Vento region of Northern Italy over 17 years, 1.8% (n=621) were identified with a cardiac condition and subsequently excluded from sport. Of these, 0.07% (n=22) were diagnosed with HCM, all of whom remained alive at follow-up. The majority of athletes excluded were as the result of hypertension, valvular heart disease, or cardiac conduction disease. The same Italian group have published data examining the efficacy of their screening program, described across three time periods – which they have termed "pre-screening" (1979-1981), "early screening" (1982-1992), and "late screening" (1993-2004). They demonstrated a reduction in sudden deaths during sport from 3.6/100,000 person-years in 1979-80, to 0.9/100,000 person years in 2003-2004 (Figure 1.9). The reduction in mortality can be explained by

a reduction in observed deaths primarily due to cardiomyopathy, including AVRC and HCM.[13]

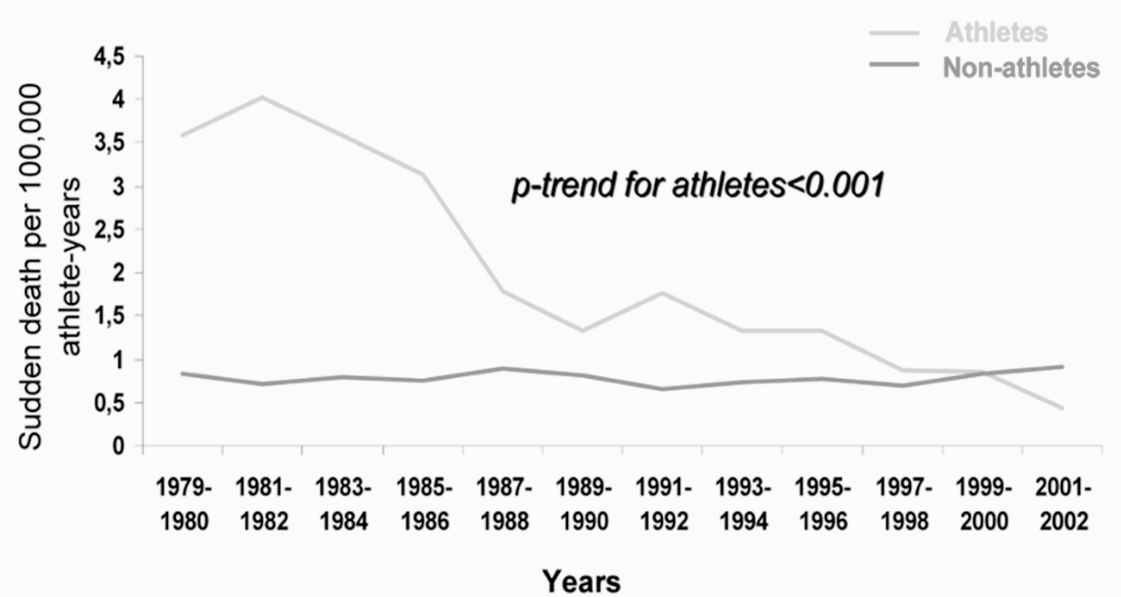

Figure 1.9 Annual Incidence Rates of Sudden Cardiovascular Death in Screened Competitive Athletes vs Non-athletes in the Veneto Region of Italy (1979-2004), demonstrating the efficacy of the addition of an ECG to the pre-participation screening protocol. Corrado et al[13]

If therefore the ECG (and subsequent echocardiogram) is to be used as tool to identify latent pathology in athletes, then it is vital that the sports cardiology community has a clear and accurate understanding of what constitutes a normal ECG across the athletic demographic spectrum.

1.4.2 The Pre-Participation screening of Black Athletes

Currently, when assessing a young black athlete, a physician is required to extrapolate data derived from a population which is non-representative for the vast majority of athletes in the United Kingdom or Western Europe. There is no data available on the ECG or echocardiogram in female black athletes to allow accurate assessment of these individuals and differentiate physiological adaptation from pathological causes of sudden cardiac death during sport. There is also no data on the longitudinal significance of the ECG changes that have been described in black male athletes,[18,53,54], and it is currently unclear if a proportion of these individuals may harbor an occult cardiomyopathy.

Worldwide sporting organizations[14,15] and international cardiac societies[17] are increasingly recommending and requiring pre-participation cardiac screening for all athletes prior to competing in international sporting events, irrespective of their nationality. This is as a result of partly an increased understanding of the disease processes that may lead to sudden death in sport and advances in the therapy of such conditions[60], and partly due to the relative success of systematic pre-participation screening programs in countries such as Italy.[13]

Along with the increase in pre-participation cardiac screening seen across sporting disciplines, there has been an overall increase in the numbers of black participants in elite sport. Within western countries, black athletes form an increasingly large percentage of all athletes representing their respective nations. For example, at the Beijing Olympics 2008, over 80% of all track and field medals were won by athletes of African/afro-Caribbean ancestry. In

particular, female black athletes won 72% of track medals at these games.[80] This is in addition to the rise of African teams competing with great success at international level in a variety of sports – in particular football, basketball, rugby and athletics. Within American sport, black players predominate within the National Football League (the NFL), and the National Basketball Association (the NBA), where 70% and 85% respectively, of players are black. Within female professional sport, two black female players have dominated the game of tennis for the last decade (the Williams sisters) and have inspired a new wave of black female players into the game. Similarly, in international track athletics, black male and female athletes have come to predominate in the upper levels of competition across both sprinting and distance running disciplines.

In general, the numbers of black participants in all sports (both male and female) over the coming decades is predicted to rise. In particular, the numbers of black female participants in organised competitive sport is expected to increase dramatically. US federal legislation - known as Title IX, has meant that sporting scholarships within the US collegiate system has to be seen to be divided equally between both male (who currently dominate college sport) and females. As a direct consequence, there has been increased opportunity for women of all races to participate in a wide range of sporting disciplines. Female participation in collegiate sport has risen by 450% across a 27 year period (1977-2006), and this trend has continued.[81] Certain sports, such as swimming, are actively targeting the black community to increase participation – currently at low levels.[82] The rise in black female athletes will be mirrored by an increase those undergoing pre-participation screening.

There is currently no data within the scientific literature on the normal electrocardiographic or echocardiographic appearances in black female athletes. If data from white athletes is incorrectly applied to this population, then there is a risk of inaccuracies in the identification and diagnosis of conditions that may predispose an individual to sudden cardiac death during sporting activities. If an incorrect diagnosis is made, and that female athlete subsequently excluded from further sporting participation, then there is potential for significant harm, both financially and psychologically. The converse is also true, with black female athletes who may harbour potentially life threatening disease placed at further risk by continued participation in sporting activity.

There is also limited data on the relationship between the ECG and echocardiographic appearances of male black athletes and potential causes of sudden death during sport - in particular. cardiomyopathy. The small volume of data currently available has concluded that the ECG repolarisation changes and echocardiographic LVH seen amongst black male athletes can be attributed to the physiological effect of training. There is no large scale descriptive or longitudinal data to confirm or refute this hypothesis. Black athletes with such ECG and echocardiographic anomalies may be falsely reassured that they do not have an occult cardiomyopathy.

It is crucial that cardiologists develop a clear and accurate understanding of the physiological adaptive processes that accompany regular systematic physical training. This should be across the demographic spectrum, with recognition that

ethic differences exist in the presentation of cardiac disease. Physicians will then be better placed to correctly assess individual athletes and prevent unnecessary exclusion of athletes, whilst identifying those at genuine increased risk of sudden death during sport.

1.5 Aims and Objectives

There are current deficiencies in the scientific literature with respect to the physiological manifestations of athlete's heart in black (African/Afro-Caribbean) athletes. In particular, there has been no published data on either the ECG or echocardiogram amongst female elite black athletes. There is also no data assessing the significance of the ECG and echocardiographic appearances that have been described amongst black male athletes.

This thesis aims to address this issue by examining the characteristics of physiological cardiac adaptation in a large unselected cohort of elite female and male athletes of African/Afro-Caribbean origin, and comparing them to both sedentary controls, similar cohorts of unselected Caucasian athletes, and a cohort of black patients who have the diagnosis of hypertrophic cardiomyopathy. Therefore the objectives of this study are to:

1. Describe the normal range of trans-thoracic echocardiographic appearances amongst female elite black athletes
2. Describe the electrocardiographic appearances seen in female elite black athletes
3. Correlate the electrocardiographic appearance amongst these two group of athletes with the trans-thoracic echocardiographic appearance
4. Compare the electrocardiographic and electrocardiographic appearances of a large cohort of male black athletes and a cohort of

black patients with HCM, in particular the significance of T-wave inversions..

5. Assess the longitudinal significance of the electrocardiographic and echocardiographic appearance in black male athletes.

Overall, the objective is to provide information regarding the normal appearance of the athlete's heart in black athletes, in order to facilitate the clear and accurate pre-participation screening of these individuals for causes of sudden cardiac death during sport.

Chapter 2 - Methodology

2.1: Setting

This study was part of a collaborative programme between the United Kingdom and France designed to investigate cardiac adaptation in black athletes. Neither country has a mandatory pre-participation cardiac screening program. However, certain international and national sporting organisations such as the International Olympic Committee[14], the Federation Internationale de Football Association (FIFA)[15], the Union Cycliste International (UCI), and the International Rugby board (IRB) require pre-participation cardiac screening for all athletes who compete at events endorsed by these governing bodies. In addition athletes who are not affiliated with these organisations but participate in the Commonwealth games are also required to undergo mandatory pre-participation screening.

Over the period of the study, our collaborative group (in conjunction with the charity Cardiac Risk in the Young (CRY) and the University Rennes Sports Institute) has been responsible for the majority of cardiac screening carried out on elite athletes in both the United Kingdom and France. In the United Kingdom this is conducted at national sporting training camps, King's College Hospital (2007-2010), University Hospital Lewisham, and St Georges Hospital (2010 onwards). In France, the majority of athlete assessment takes place at the Sports Medical Institute of the University Hospital Rennes, under the supervision of Prof. F Carre. The data presented here represents the sum of all

available athletes that have been assessed as part of the ongoing work of the group across both countries between 2006 and 2010.

2.2 – Study Design

This study was undertaken as a prospective cohort study, examining the ECG and echocardiographic appearances of a group of elite African/Afro-Caribbean athletes. The findings were compared to a similar group of elite Caucasian athletes, a similar group of sedentary African/Afro-Caribbean sedentary control subjects, and a group of patients who had been diagnosed with hypertrophic cardiomyopathy.

Ethical approval for this work was granted by the ethics committee at the University Hospital Lewisham and South East Thames ethics committee's and in France, by the University Rennes Ethics Board. Information sheets were provided to all athletes, controls, and HCM patients at least 24 hours prior to the assessment that clearly explained the screening process (Appendix A). Medical staff were available to answer any specific questions that the subjects may have prior to the assessment taking place. All study participants provided written consent for the evaluation.(Appendix B)

2.2.1: Subjects

Between 1996 and 2010, 3185 consecutive athletes, 399 sedentary control subjects and 155 patients with hypertrophic cardiomyopathy underwent assessment with a health questionnaire, focused cardiac examination, 12-lead

ECG and 2-dimensional echocardiogram. Amongst the athletes and controls, the assessment was part of a standard pre-participation cardiac screening. In the individuals with HCM, the assessment formed part of the standard ongoing clinical assessment in a number of outpatient clinics run from a tertiary cardiology referral centre in South London.

2.2.1.1 Athletes

An athlete was defined as an individual who participates and competes in a singular sporting discipline on a regular basis.

Athletes were recruited from consecutive screenings organised on behalf of various national sporting governing bodies – including the FA, the IRB, the British Olympic Association (BOA), the Comite National Olympique et Sportif Francais, and the Lawn Tennis association (LTA). All athletes were fully consented to participate at the time of screening. All athletes competed at regional, national or international level. All athletes underwent at least one standard pre-participation cardiac evaluation.

In total, 440 female athletes and 2745 male athletes were assessed, in both the U.K. and in France.

2.2.1.2 Sedentary controls

A sedentary control subject was defined as an individual who performs less than 2 hours per week of regular purposeful physical activity.

Sedentary controls were recruited from the voluntary cardiac screening program run by the charitable body, Cardiac Risk in the Young (CRY). The service offered is freely available to the general public, irrespective of their athletic prowess or participation. The standard CRY screening in the majority of cases comprises a focused history, examination and ECG, with an echocardiogram only if indicated. In total, 7326 individuals underwent cardiac screening between 2006 and 2010. Any potential selection bias was minimised by considering only consecutive individuals who attended screening events offering both ECG and echocardiography as cardiac investigations. All controls were consented to participate at the time of screening, and all groups were assessed using identical screening protocols. Further selection criteria included an ethnic background defined as white or black (African/Afro-Caribbean), age 14 to 35 years old, the absence of cardiac symptoms, drug history , or family history of sudden cardiac death or cardiomyopathy. In total, 399 individuals where included in the analysis, 119 black male controls, 140 black female controls, and 140 white female controls. For the purposes of this study, individuals hailing from other ethnic groups (e.g. asian or chinese descent) were excluded.

2.2.1.3 Hypertrophic Cardiomyopathy patients

Between 2001 and 2010, 155 new patients with hypertrophic cardiomyopathy were seen and assessed in one of three specialist cardiomyopathy clinics in South London. These institutions include Kings College Hospital, University Hospital Lewisham, and St Georges Hospital. The particular demographic characteristics of the community served by these hospitals comprises of a substantial proportion of individuals of African/Afro-Carribean descent. In some areas, this approaches 30%, compared to a national average of under 2%.

These clinics, therefore, offered a unique environment to identify black individuals, both male and female, that are affected by HCM. The majority of patients diagnosed with HCM were referred originally from primary care following symptoms (including chest pain, palpitations, and breathlessness), the identification of a new cardiac murmur, or for screening in the context of a family history of HCM or sudden cardiac death. A further cohort of patients were referred from local district hospitals seeking a specialist opinion.

The diagnosis of HCM was made based upon the AHA/ESC consensus statement. [42,60] In general, the condition was identified based on a maximal end-diastolic left ventricular wall thickness of greater than 15mm in any myocardial segment, in the absence of a cardiac or systemic cause, or the identification of relative left ventricular hypertrophy (a maximal left ventricular wall thickness between 12 and 15mm) with electrocardiographic abnormalities consistent with HCM (repolarisation abnormalities, extreme leftward axis deviation, of left bundle branch block) and the identification of HCM in a first

degree relative. Only patients with African/Afro-Caribbean ancestry were considered for this analysis. Patients who had previous been subjected to therapy that may induce significant ECG changes - most notably repolarisation anomalies - such as septal myomectomy or pacemaker insertion were excluded, as were patients who had a concurrent diagnosis of myocardial ischaemia that may have affected the pattern of the 12-lead ECG. A total of 52 patients, 32 mean and 20 women, fulfilled the inclusion criteria and were included in this analysis.

2.2.3. Health Questionnaire

The health questionnaire (appendix C) has been designed to specifically assess symptoms that may be the result of previously unrecognised pathological cardiac disease.[83] It asks for information on past medical and drug history, family history -including established risk factors for the development of atherosclerosis (hypertension, diabetes, and hypercholesterolaemia), and information on any specific incidences of sudden death in young family members (either as a result of a specific cardiac cause or unexplained).

Any athlete or control with specific cardiac symptoms which raised suggestion of occult cardiac disease, or family history of sudden cardiac death or a hereditary disease which may predispose an individual to sudden cardiac death during sport, were excluded from further analysis and investigated appropriately in a tertiary cardiology clinic.

All subjects were then asked to define their main sport in which they participate (if any) and state the number of hours that total training in an average week. A sedentary control subject was defined on the basis of this self reported figure. To be considered as sedentary, an individual had to state that they participated in less than 2 hrs per week of regular sporting activity.

2.2.3 Demographic Data Collection

Each subject's age at the time of screening, height and weight were recorded. The subjects were requested to remove excess clothing and all footwear. Height was measured using a standard stadiometer, and recorded (to the nearest cm). The subject's weight was then recorded to the nearest kilogram. Weight was measured using a scale (Seca, Hamburg, Germany) that had been calibrated regularly. Body surface area (BSA) was calculated using the formula – BSA (m^2) = 0.20247 x Height(m)$^{0.725}$ x Weight(kg)$^{0.425}$.[84]

The subject were asked to self define their ethnicity, with terms including black African, black Afro-Caribbean, black British, black French, white British, white Irish and white French. These were then collated – with the term "black" in this study being used to describe an individual of African or Caribbean islands in descent. [85,86]

2.2.4 Clinical Examination

Each subject underwent a focused cardiac examination, including blood pressure measurement, and auscultation of the precordium, according to the ESC consensus statement on pre-participation screening. [17]

Blood pressure was measured using a manual sphygmomanometer at rest. If elevated, then this was repeated on three occasions and an average taken, in an attempt to account for any potential hypertensive stress response. Athletes or controls with persistent hypertension were referred to their general practitioner for ongoing monitoring and investigation as appropriate.

Results were documented, and any athlete or control with examination findings clearly consistent with an occult cardiac disease were excluded from further analysis and investigated appropriately in a tertiary centre cardiology clinic.

Of the full cohort of 3584 individuals without a diagnosis of cardiomyopathy, 22 athletes (all male) were excluded based on systolic blood pressure readings of greater than 140mmHg or diastolic blood pressure readings of greater than 90mmHg.

2.2.5 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (EKG) was performed during quiet respiration in a supine position using a Philips Pagewriter Trim III ((Philips, Bothel, Washington) recorder.[87] The electrodes were placed carefully to

ensure consistency, and ECGs were recorded at a paper speed of 25 mm/s. Heart rate and QRS axis were calculated. A significant left QRS axis was defined as a frontal axis between -30^{o} and -90^{o} .P, Q-, R-, S-, and T-wave voltages; ST-segments; QRS duration; PR interval; and QT-interval were measured in each lead using callipers. Pathological Q-waves were defined as being greater than 0.04s in duration or ≥25% of the height of the following R-wave. The QT-interval was corrected for the heart rate (QTc) using the Bazzet's formula.[54] Electrocardiographic LVH was defined using the Sokolow–Lyon voltage criterion.[88] Electrocardiographic criteria for left and right atrial hypertrophy were defined according to the European Society of Cardiology (ESC) consensus statement on pre-participation screening.[16,17]

ST segment shift and T wave inversions were considered as repolarisation anomalies. ST segment deflection was considered significant if ≥1mV in 2 or more contiguous leads. Similarly, T wave inversion of ≥-0.1mV in 2 or more contiguous leads was considered significant - excluding that seen in lead aVR, V1 and lead III in isolation. Biphasic T waves were considered abnormal if the negative portion exceeded -0.1mV. If present, the distribution of T wave inversions was classified into one of three groups:

- T wave inversions affecting the Anterior leads (V1-V4)
- T wave inversions affecting the inferior leads (II, III, aVF)
- T wave inversions affecting the lateral leads (I, aVL, V5, V6)

Deep T wave inversions were defined as a maximal negative deflection of -0.2mV or greater, in at least one lead, in an ECG that demonstrates significant T-wave inversions (i.e. in 2 or more contiguous leads).

All ECGs were read and interpreted by myself, and validated by two senior physicians, in the UK and France, both of whom are highly experienced in sports cardiology and the diagnosis and management of HCM.

2.2.6 Trans-thoracic Echocardiography

A full 2-dimensional echocardiogram was conducted on each subject by one of 3 experienced sports cardiologists (the majority by myself) using GE Vivid I (General Electric, Tirat Carmel, Israel), Philips Sonos 7500, or Philips CPX50 (Philips, Bothel, Washington) cardiac ultrasound equipment. Standard views of the heart were obtained, and analysed according to the protocol specified by the European Society of echocardiography.[89] Left ventricular (LV) wall thickness was measured in the 2-dimensional para-sternal short axis, at the levels of the mitral valve and papillary muscles; the greatest measurement being defined as the maximal LV wall thickness (maximal LVWT). Left ventricular diameter was measured in the para-sternal long axis using an M-mode positioned at the tips of the mitral valve leaflets, according to the ESC protocol.[89] If the M-mode cursor could not be positioned on axis, then a 2-D image was used for assessment. Left atrial diameter was measured in the the para-sternal long axis at end-diastole. Aortic annular size was also measured using an M-mode cursor, positioned parallel to the cusps of the aortic valve in the para-sternal long axis.[89] Left ventricular mass (LVM) was calculated using the formula of Devereux.[90] Left ventricular ejection fraction was calculated from left ventricular volumes using Simpson's rule[91]. Assessment of diastolic function included traditional pulsed wave Doppler across the mitral valve,[67] and

tissue Doppler velocity imaging of the septal and lateral mitral valve annulus.[70] Echocardiographic files were saved to compact disc or digital video disk as numeric files to preserve anonymity.

All measurements where repeated by an experienced senior cardiologist, blinded to the identity of the subject.

2.3 Further Evaluation and follow-up

All subjects with left ventricular hypertrophy (maximal LVWT of > 11 mm) or T wave inversions in 2 contiguous leads underwent further clinical evaluation with treadmill exercise testing, 48hr Holter monitoring and where appropriate, cardiac magnetic resonance imaging to check for the broader phenotypic features of the variety of cardiac diseases that may pre-dispose individuals to sudden cardiac death during sport. [59]

Several athletes underwent repeat cardiac evaluation over the time period of the study, in accordance with the screening policies of their sporting organisations. The timetable of such evaluations was dictated according purely by the sporting organisation concerned, and was irrespective of baseline results.

2.3.1: Exercise stress testing

An upright treadmill stress test was performed using the standard Bruce Protocol.[92] EKG and blood pressure (BP) were recorded at 1min intervals.

Subjects were exercised to volitional exhaustion and assessed specifically for the development of ischaemic changes, abnormal or flat BP response and arrhythmias. An abnormal blood pressure response was defined as a rise in systolic blood pressure from resting baseline to peak exercise of less than 25mmHg or a fall of 10mmHg or more from baseline, or the peak blood pressure attained.[93]

2.3.2: 48-Hour ECG monitoring

48 hour ambulatory ECG monitoring was performed to check specifically for supra-ventricular and/or ventricular tachy-arrhythmias.[94] Athletes were encouraged to continue usual day-to-day life activities including exercise during the investigation.

2.3.3: Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging was performed with a Siemens Sonata 1.5T (Erlangen, Germany) using steady-state, free precession breath-hold cines (TE/TR 1.6/3.2 ms, flip angle 60°) in long-axis planes and sequential 7mm short-axis slices (3mm gap) from the atrioventricular ring to the apex. Late gadolinium enhancement images were acquired 10 minutes after intravenous gadolinium-DTPA (Schering, 0.1mmol/kg) in identical short-axis planes using an inversion-recovery gradient echo sequence. Inversion times were adjusted to null normal myocardium (typically 320 to 440 ms; pixel size 1.7 x 1.4mm). Late gadolinium enhancement images were phase swapped to exclude artefact. Ventricular volumes and function were measured for both

ventricles using standard techniques[95,96] and analyzed using semi-automated software (CMR tools, Cardiovascular Imaging Solutions, London, UK). All volumes and masses were indexed for age and BSA

2.4: Statistical Analysis

Data are expressed as mean ± standard deviation (SD), with percentages were appropriate. Variables were tested for normality using the Kolmogoriv-Smirnov test. Statistical analyses to assess group differences were performed using unpaired Students t-test or one-way ANOVA and Mann-Whitney U or Kruskal-Wallis tests for normally and non-normally distributed variable respectively. To test group differences in proportions, Fisher's exact test was used, calculated from a 2 x 2 contingency table using SPSS version 12 (Chicago, IL, USA). A p value of <0.05 was considered significant for all statistical analyses.

For continuous variables, a stepwise multivariable linear regression model was constructed to assess the relationship between LVWT and LVM, as dependant variables, with age, height, weight, body surface area, ethnicity, country of screening and hours trained as predictors.

For binary variables, a binary logistic regression model was constructed to assess any relationship between T-wave inversions or ST segment elevation as dependant variables, and age, height, weight, BSA, country of screening, number of hours trained, ethnicity, maximal LVWT, and end diastolic left ventricular cavity diameter as independent variables.

Averaged coefficients of variance for intra-observer and inter-observer variability were calculated for values of maximal left ventricular wall thickness. No attempt was made to re-test, as the the observed variability in measures was low - see chapter 4, section 4.4.

Chapter 3 – Subject Characteristics

In total, 3562 individuals underwent assessment as part of this study. The subject characteristics will be presented below, divided according to gender.

3.1 Female Subject Demographics

In total, 240 consecutive female black and 200 Caucasian athletes and 140 consecutive black and 140 Caucasian sedentary female control subjects underwent assessment.

3.1.1 Black Female Athlete Demographics

Two hundred and forty consecutive black female athletes were recruited from a variety of sporting disciplines. These included athletics (25%), basketball, (20%), football/soccer (16%), netball (18%) and martial arts(13%) (Table 3.1). They reflect the typical sports in which black female athletes participate in Western Europe.

The demographics of the black female athlete group is presented in table 3.1. Of the 240 black athletes, 70% (n=169) originated from the UK, and the remainder from France. On average, each athlete participated in their chosen sporting discipline for 13.7±3.4 hrs (8-24hrs) per week. All athletes competed at regional, national or international level.

3.1.2 White Female Athlete Demographics

Two hundred consecutive white female athletes were recruited from the same sporting disciplines as the black athletes (Table 3.1). In general, the athletes were recruited from the same clubs and teams as the black athletes, and therefore participated in similar training programes.

White female athletes were similar in age, height and weight to the black female athlete group (Table 3.1). Of the two hundred white female athletes, 70% (n=140) were studied in the UK, with the remainder in France, an identical proportion as within the black female athletic group. On average, each athlete participated in their chosen sporting discipline for 14.4±6.1hrs (8-36hrs) per week. All Caucasian female athletes participated at a similar competitive level to the black female athlete group – with each athlete having competed at regional, national or international level.

Table 3.1. Demographic characteristics of Female Black and White Athletes

	BLACK ATHLETES (n=240)	WHITE ATHLETES (n=200)	P VALUE
Age (years)	21±4.6 (14-35)	20±4.0 (14- 35)	**0.18**
Weight (kg)	66±10.8 (39-106)	64±8.4 (45-92)	**0.06**
Height (m)	1.71±8.3 (150-192)	1.70±7.7 (151-191)	**0.07**
BSA (m^2)	1.78±0.17 (1.31-2.21)	1.73±0.18 (1.33-1.96)	**0.10**
Resting SBP (mmHg)	110±19 (120-80)	111±13 (120-80)	**0.80**
Resting DBP (mmHg)	65±12 (85-40)	66±12 (89-40)	**0.94**
Training/week (Hours)	13.7±3.4 (8-24)	14.4±6.1 (8, 36)	**0.41**
Sporting discipline			
Athletics (%)	25	23	**0.58**
Basketball (%)	20	18	**0.63**
Football (Soccer) (%)	16	20	**0.26**
Netball (%)	18	18	**1.00**
Martial arts (%)	13	11	**0.56**
Other (%)	8 (n=19) LDR n=8 Fencing n= 3 Handball n=3 Weightlifting n=3 Hockey n=2	10 (n=20) LDR n=10 Fencing n=2 Handball n=2 Weightlifting n=2 Hockey n=4	**0.50**

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate.

Abbreviations –BSA – Body Surface Area, DBP – Diastolic Blood Pressure, LDR – Long Distance Running, SBP – Systolic Blood Pressure.

3.1.2 Female Control subject Demographics

One hundred and forty consecutive black female sedentary control subjects and 140 female sedentary white control subjects were recruited from CRY screening clinics, conducted within the UK. All controls participated in less the two hours of sporting activity per week (Table 3.2). When comparing control groups, both black and white female sedentary subjects were similar and comparable in all demographic characteristics. (Table 3.2).

Table 3.2 Demographic Characteristics of Black and White Female Control Subjects

	White Controls	Black Controls	P Value
Age (yrs)	20±5.3 (14-35)	21±6.6 (14-35)	**0.07**
Height (cm)	168±6.6(154-187)	1.69±6.9 (1.5-1.87)	**0.08**
Weight (Kg)	64±13.6(37-106)	65±13.4 (42-109)	**0.6**
BSA (m^2)	1.71±0.17(1.3-2.1)	1.74±0.17(1.3-2.2)	**0.34**
SBP(mmHg)	111±15 (120-80)	113±13(120-80)	**0.29**
DBP (mmHg)	65±12 (87-40)	65±15 (80-40)	**0.94**
Training/week (hrs)	1.22±0.83(0-2)	1.1±0.85(0-2)	**0.57**

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate.

Abbreviations –BSA – Body Surface Area, DBP – Diastolic Blood Pressure, LDR – Long Distance Running, SBP – Systolic Blood Pressure.

3.1.3 Female Athletes versus Control subjects

When compared to their respective control groups, both black and white female athletes were similar in age, height, weight, and body surface area. There were no significant differences in systolic or diastolic blood pressure between the athlete and control groups. (Table 3.3 – White female athletes vs. white female controls, Table 3.4 – Black female athletes vs. black female controls).

By definition, both groups of athletes spent a significantly greater amount of time engaging in physical activity when compared to sedentary controls. (Table 3.3/3.4)

Table 3.3 Demographic characteristics of black female athletes and controls

	Black Athletes	Black Controls	P Value
Age (yrs)	21±4.6 (14-35)	21±6.6 (14-35)	**0.37**
Height (cm)	1.71±8.3 (1.5-1.92)	1.69±6.9 (1.5-1.87)	**0.07**
Weight (Kg)	66±10.8 (39-106)	65±13.4 (42-109)	**0.18**
BSA (m^2)	1.78±0.18 (1.3-2.2)	1.74±0.17(1.3-2.2)	**0.06**
SBP(mmHg)	110±19 (120-80)	113±13 (120-80)	**0.40**
DBP (mmHg)	65±12 (85-40)	65±15 (80-40)	**0.32**
Training/week (hrs)	13.7±3.4 (8-24)	1.1± 0.85 (0-2)	**<0.0001**

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate.

Abbreviations –BSA – Body Surface Area, DBP – Diastolic Blood Pressure, LDR – Long Distance Running, SBP – Systolic Blood Pressure.

Table 3.4 Demographic characteristics of white athletes and controls

	White Athletes	White Controls	P Value
Age (yrs)	20±4.0 (14- 35)	20±5.3 (14-35)	**0.46**
Height (cm)	1.70±7.7 (151-191)	168±6.6(154-187)	**0.27**
Weight (Kg)	64±8.4 (45-92)	64±13.6(37-106)	**0.97**
BSA (m^2)	1.73±0.18 (1.33-1.96)	1.71±0.17(1.3-2.1)	**0.49**
SBP(mmHg)	111±13 (120-80)	111±15 (120,80)	**0.90**
DBP (mmHg)	66±12 (89-40)	65±12 (87-40)	**0.34**
Training/week (hrs)	14.4±6.1 (8, 36)	1.22±0.83(0-2)	**<0.001**

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate.

Abbreviations –BSA – Body Surface Area, DBP – Diastolic Blood Pressure, LDR – Long Distance Running, SBP – Systolic Blood Pressure.

3.2 Male Subject Demographics

In total, 904 black male athletes, 1829 white male athletes, and 119 black male control subjects underwent assessment as part of this study.

3.2.1 Black male Athlete demographics

Black male athletes were recruited from a variety of sporting disciplines (Figure 3.1). In total, 25 sporting disciplines were studied, including soccer (41%), track and field athletics (18%), boxing (15%) and martial arts (9%)(Figure 3.1). These sports reflect the typical participation levels in western europe. Black male athletes exercised for a longer period of time per week than white male

athletes (15.2 ± 6.1 vs 13.1± 6.2 hrs/week). (Table 3.5). Every effort was made to recruit athletes from the same teams/coaching organisations in order to ensure that similar training programmes were pursued by athletes from different ethnic backgrounds, participating in the same sport.

When compared to white male athletes and black male controls, black athletes were older (with 95% being over 16 yrs old; Black males 22.5±5(14-35) yrs vs white male athletes 17.4 ± 4.1 (14-35 yrs); $p<0.001$)), and had a higher body surface area. (Table 3.5) Systolic and diastolic blood pressure and was also higher in black male athletes than in white male athletes (Table 3.5).

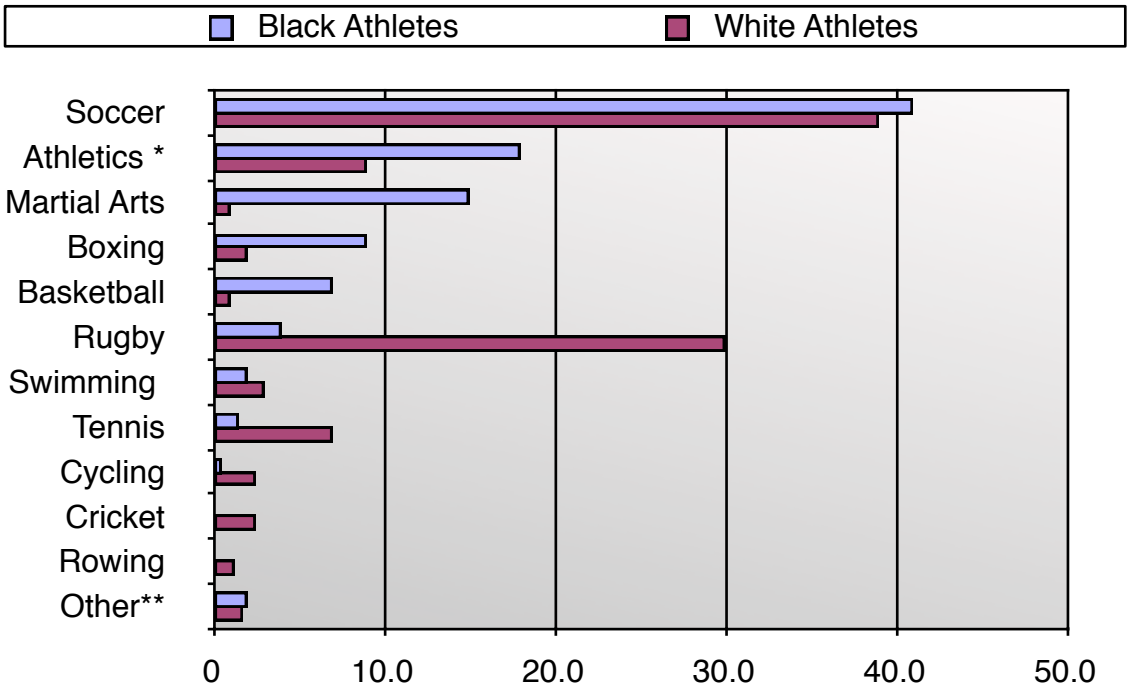

Figure 3.1 Sporting Disciplines expressed as percentage of the total black (Black bars) and white (grey bars) athlete cohorts respectively. *Track and Field events. **<1% of the total cohort. White athletes: Biathlon n=15; speed skating n=10; Gaelic Football n=7; badminton n=5. Black athletes: weight lifting n=6; American Football, n=5; gymnastics n=5; fencing n=5.

Table 3.5 Demographic Characteristics of Male Athletes and Controls

Parameter	Black Athletes	White Athletes	Black Controls	P-value
N=	904	1819	119	
Age (yrs)	22.5 ± 5.0 (14-35)	17.4 ± 4.1 (14-35)	18.6 ± 6.0 (14-35)	<0.001 [a,b,c]
BSA (m^2)	1.92 ± 0.2 (1.3-2.8)	1.87 ± 0.24 (1.27-2.8)	1.87 ± 0.24 (1.3-2.6)	<0.001 [a,b]
Systolic BP (mmHg)	116.5 ± 13.1 (80-140)	111.8 ± 11.0 (82-145)	121.7 ± 8.4 (90-140)	<0.001 [a,b,c]
Diastolic BP (mmHg)	71.2 ± 11.5 (40-90)	68.9 ± 9.6 (40-89)	74.2 ± 8.5 (56-85)	0.002 [a] <0.001 [b,c]
Hours Trained (h/week)	15.2 ± 6.1 (8-36)	13.1 ± 6.2 (8-30)		<0.001 [a,b,c]

[a]Statistically significant difference between black athletes and white athletes

[b]Statistically significant difference between black athletes and black controls

[c]Statistically significant difference between white athletes and black controls.

3.2.2 White male athlete demographics

In total, 1819 consecutive white male athletes were recruited from a variety of sporting disciplines which is summarised in figure 3.1. In general, white male athletes were recruited from the same teams/training organisations as black male athletes. The distribution of sporting disciplines and rates of participation reflects general participation levels by black and white male individuals across the UK and France. All athletes participated at regional, national or international level in their chosen sporting discipline.

The demographic characteristics of the cohort of white male athletes is shown in Table 3.5. When comparing white athletes to black controls, white male athletes were younger but of similar body surface area. White male athletes also exhibited lower levels of both systolic and diastolic blood pressure (Table 3.5).

3.2.3 Black male sedentary control subjects

In total, 119 consecutive black sedentary control subjects were assessed over the study period. All subjects participated in less than 2 hours of regular physical activity per week. Their demographic characteristics are summarised in table 3.5.

Black male sedentary individuals were younger than black athletes, but older than white athletes (Table 3.5). They exhibited a lower body surface area, but higher systolic and diastolic blood pressure where compared to black male athletes (Table 3.5).

3.3 Patients with Hypertrophic Cardiomyopathy

In total, 52 consecutive black patients with hypertrophic cardiomyopathy underwent assessment using the standardised cardiac screen described in chapter 2. the demographic and clinical characteristics are summarised in table 3.6.

The average age of diagnosis was 48.1 ± 17.1 yrs, and the majority of patients were male(61.5%). All were diagnosed and assessed in the UK in one of 3 specialist cardiomyopathy clinics in South East London.

A minority of patients had a family history of Hypertrophic cardiomyopathy or sudden cardiac death (34.6%). 5.8% of individuals seen had an ICD in situ, implanted as a consequence of an aborted sudden cardiac death or clinical features that suggest a high risk of such an event occurring (according the ACC/ESC task force criteria). Over 50% of patients were on some form of pharmacotherapy to alleviate symptoms and/or to treat arrhythmias (Table 3.6)

Table 3.6 Demographic and clinical characteristics of black patients with HCM

	Black HCM Patients (n=52)
Demographic and Clinical characteristics (%)	
Age at diagnosis (years)	48.1 ± 17.1
Gender (males)	61.5
Family history of HCM/SCD	34.6
Patients on Treatment	51.9
B-Blockers	26.9
Calcium Channel antagonists	26.9
Amiodarone	7.7
Disopyramide	3.8
Diuretics	17.3
ICD* in situ	5.8

*ICD - Implantable Cardiac Defibrillator

3.5 Screening Questionnaire Results

All athlete and control subjects (male and female) were assessed using the same standardised health questionnaire (Appendix C).

No healthy athlete or control subject documented symptomatic information that could be consistent with a history of occult cardiac disease, either via questionnaire or upon further questioning during the screening process. None volunteered any significant past medical history, and no subject was prescribed any regular cardiac medication.

No healthy subject (i.e. without a diagnosis of hypertrophic cardiomyopathy) reported any family history of sudden cardiac death or cardiomyopathy.

No individual reported any family history of hypertension, hypercholesterolemia or diabetes in first degree family members. No attempt was made to further question the individuals assessed beyond the questionnaire unless this highlighted an area of concern.

3.6 Examination findings

No athlete or healthy control had any significant findings on physical examination. None had any signs consistent with any potential inherited causes of sudden cardiac death. The majority of athletes and controls were normo-tensive, with a blood pressure of <140/80. 5 individuals, all male, were

excluded from the study due repeated blood pressure measures of >140/80mmHg

3.7 Conclusion

All athletes and control subjects were subject to the same initial screening protocol, based on clinical history and examination. No individual without a prior diagnosis of cardiomyopathy demonstrated any clinical findings that would be consistent with occult cardiac disease that may put an individual at risk of sudden death during sporting activity.

Chapter 4 – Trans-thoracic echocardiography in Elite female athletes – The impact of ethnicity and sporting participation.

This chapter aims to describe the characteristics of cardiac adaptation in elite black female athletes, as seen on trans-thoracic echocardiography. The echocardiographic findings in two hundred and forty elite black female athletes were compared with 200 similar Caucasian female athletes, 140 sedentary black female control subjects, and 140 sedentary white female controls, a total of 720 female subjects. The demographic characteristics of both athlete and control groups are described in detail in Chapter 3

4.1. Left Ventricular Dimensions

This first section describes the echocardiographic dimensions and functional characteristics of the left ventricle in both female athletes and female control subjects.

4.1.1 – Control Subjects (Table 4.1)

Both black and white female control subjects exhibited similar left ventricular dimensions. There was no significant difference seen in maximal left ventricular cavity diameter in either diastole (Table 4.1). With respect to measures of left ventricular size, both groups had similar values of inter-ventricular septal wall thickness, posterior wall thickness, and maximal left ventricular wall thickness. Calculated values of left ventricular mass were also similar between the two

groups (Table 4.1). None of the control subjects had evidence of left ventricular cavity enlargement (>54mm) at end-diastole.

All control subjects had normal indices of systolic and diastolic function. There were no demonstrable differences in either between black and white control subjects.

Table 4.1 Comparison of echocardiographic cardiac dimensions between black and white female control subjects

	BLACK CONTROLS (n=140)	WHITE CONTROLS (n=140)	P VALUE
Ao (mm)	25.7±3.8 (19-32)	24.9±3.4(19-32)	0.46
LA (mm)	30±4.2 (22-38)	31±4.7(20-40)	0.69
LVED (mm)	44.7±3.9(34-52)	45.5±4.1(36-52)	0.32
LVES (mm)	28.2±3.9(22-36)	29±3.9(21-37)	0.41
IVSd (mm)	8.1±1.4(6-11)	8±1.1(6-11)	0.73
PTWD (mm)	7.9±1.2(6-11)	7.8±1(6-11)	0.65
Max LVWT (mm)	8.4±1.4(6-11)	8.1±1.1(6-11)	0.33
LVM (g)	143±34(61-206)	145±31(73-206)	0.75
E wave (m/s)	0.93±0.15(0.5-1.2)	0.92±0.2(0.5-1.42)	0.74
A wave (m/s)	0.44±0.16(0.2-0.9)	0.48±0.13(0.2-1)	0.17
E/A ratio	2.3±0.77(0.6-4.5)	2.04±0.69(0.7-4.5)	0.12
E` (m/s)	0.21±0.03 (0.27-0.15)	0.22±0.05(0.25-0.12)	0.45
A` (m/s)	0.06±0.04 (0.14- 0.02)	0.07±0.03(0.13-0.02)	0.52
E:E`	4.42±0.74 (5.62-1.87)	4.37±0.68(5.71-1.79)	0.23
EF (%)	65±7.2 (46-76)	65±8.4(48-79)	0.75

Data expressed as mean±standard deviation (limits).

Abbreviations for Table 4.1/4.2/4.3/4.4

A wave=late diastolic mitral valve inflow peak velocity; A`=late annular diastolic peak velocity (lateral mitral annulus); Ao=Aortic annulus diameter; E wave=early diastolic mitral valve peak inflow velocity; E`=early diastolic annular peak velocity (lateral mitral annulus); E:E`=ratio of peak early diastolic mitral inflow velocity to peak early diastolic mitral annular velocity; EF=Ejection Fraction; continued on following page.

Abbreviations for Table 4.1/4.2/4.3/4.4 continued

IVSd=maximal left ventricular septal wall thickness in end-diastole; LA=left atrial diameter; LVED=maximal left ventricular cavity dimension in end-diastole; LVES=maximal left ventricular cavity dimension in end-systole; LVM=left ventricular mass; Max LVWT=maximal left ventricular wall thickness in end-diastole; PTWd=left ventricular posterior wall thickness in end-diastole.

4.1.2 – Black female athletes versus Black female control subjects (Table 4.2)

When compared to sedentary control female subjects, black female athletes demonstrated a significant increase in left ventricular inter-ventricular septal wall thickness, posterior wall thickness, and maximal left ventricular wall thickness (Table 4.2). Overall, there was an 11% difference in maximal left ventricular wall thickness between black athletes and sedentary control subjects.

Calculated left ventricular mass was significantly greater in black athletes than black control subjects (Table 4.2) amounting to a 31% difference between the 2 groups. With respect to measures of left ventricular cavity diameter, black athletes demonstrated a significantly larger end diastolic and end systolic diameters compared with controls.

Both athletes and controls exhibited normal indices of both systolic and diastolic function, with no demonstrable differences between the two groups.

Table 4.2 Comparison of echocardiographic cardiac dimensions between Black athletes and Black control subjects

	BLACK ATHLETES (n=240)	BLACK CONTROLS (n=140)	P VALUE
Ao (mm)	27.2±2.9 (23-38)	25.7±3.8 (19-32)	**0.04**
LA (mm)	35.3±4.7 (21-45)	30±4.2 (22-38)	**<0.001**
LVED (mm)	48.6 ±3.9 (39-60)	44.7±3.9(34-52)	**<0.001**
LVES (mm)	30.8±4.0 (21-44)	28.2±3.9(22-36)	**0.003**
IVSd (mm)	9.0±1.3(6-13)	8.1±1.4(6-11)	**0.002**
PTWD (mm)	8.7±1.3(6-12)	7.9±1.2(6-11)	**0.01**
Max LVWT (mm)	9.2±1.2 (6-13)	8.3±1.4(6-11)	**0.002**
LVM (g)	187.2±42 (95-322)	143±34(60-214)	**<0.001**
E wave (m/s)	0.89±0.2 (0.6-1.36)	0.92±0.15(0.5-1.2)	0.59
A wave (m/s)	0.41±0.1 (0.2-1.1)	0.44±0.16(0.2-0.9)	0.71
E/A ratio	2.3±0.8 (1.1-5.5)	2.05±0.69(0.7-4.5)	0.17
E` (m/s)	0.22±0.03 (0.13-0.25)	0.21±0.03 (0.15-0.27)	0.39
A` (m/s)	0.07±0.03 (0.02-0.16)	0.06±0.04 (0.02-0.14)	0.45
E:E`	4.41±0.71 (2.3-5.61)	4.42±0.74 (1.87-5.62)	0.76
EF (%)	67±6.7 (41-78)	65±7.2 (46-76)	0.32

Data expressed as mean±standard deviation (limits)

Abbreviations for Table 4.2 - see pages 95/96 (as per table 4.1)

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4.1.3 - White Female athletes versus White Female controls (Table 4.3)

In a similar pattern to that observed amongst black athletes, white athletes exhibited a significantly greater inter-ventricular septal wall thickness , posterior wall thickness , and maximal left ventricular wall thickness, when compared to the group of sedentary control subjects (Table 4.3). This represents a 6% difference in maximal left ventricular wall thickness.

Calculated left ventricular mass was 19% greater amongst white athletes when compared to sedentary controls . Measure of left ventricular cavity size in both diastole and systole were greater in athletes than controls (Table 4.3).

All indices of systolic and diastolic function were normal in both groups, with no differences evident between athletes and sedentary control subjects. Amongst athletes, the peak E and A wave velocity was lower when compared to sedentary controls. WIth respect to the A wave, this reached statistical significance (P=0.001).

Table 4.3 Comparison of echocardiographic cardiac dimensions between white athletes and white control subjects

	WHITE ATHLETES (n=200)	WHITE CONTROLS (n=140)	P VALUE
Ao (mm)	26.4±3.5 (17-33)	24.9±3.4(19-32)	**0.002**
LA (mm)	32.5±2.1 (21-47)	31±4.7(20-40)	0.08
LVED (mm)	48.2±3.5 (40-62)	45.5±4.1(36-52)	**<0.001**
LVES (mm)	30.5 ±4.7 (20-44)	29±3.9(21-37)	**0.02**
IVSd (mm)	8.4±1.2 (6-11)	8±1.1(6-11)	**0.046**
PTWD (mm)	8.4±1.2 (6-11)	7.8±1(6-11)	**<0.001**
Max LVWT (mm)	8.6±1.2(6-11)	8.1±1.1(6-11)	**0.006**
LVM (g)	172.3±42 (86-293)	145±31(73-206)	**<0.001**
E wave (m/s)	0.90±0.2 (0.53-1.33)	0.92±0.2(0.5-1.42)	**0.07**
A wave (m/s)	0.44 ±0.1(0.2-0.9)	0.48±0.13(0.2-0.9)	**0.001**
E/A ratio	2.2±0.8 (1.1-5.5)	2.04±0.69(0.7-4.5)	**0.01**
E` (m/s)	0.23±0.03 (0.28, 0.17)	0.22±0.05(0.25-0.12)	0.45
A` (m/s)	0.06±0.03 (0.13, 0.03)	0.07±0.03(0.13-0.02)	0.57
E:E`	4.46±0.74 (5.55, 1.96)	4.37±0.68(5.71-1.79)	0.19
EF (%)	66±6.9 (44, 76)	65±8.4(48-79)	0.43

Data expressed as mean±standard deviation (limits).

Abbreviations for Table 4.3 - see pages 95/96 (as per table 4.1)

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4.1.3 – Black Female athletes versus White Female athletes (Table 4.4)

Black athletes demonstrated a greater maximal left ventricular wall thickness compared with white athletes amounting to a 7% difference between the two groups. Calculated LVM was also greater in black athletes vs. white athletes, with a 9% difference overall between the ethnic groups. Black athletes also demonstrated a significant increase in inter-ventricular septal wall thickness compared to white athletes. There was no significant difference in posterior wall thickness measurements between the groups.

The range of left ventricular wall thickness observed amongst white athletes and both white and black control groups was 6-11mm, compared to the range seen amongst black athletes of 6-13mm. In total, 3% of black athletes had a maximal left ventricular wall thickness of >11mm. The distribution of maximal left ventricular wall thickness amongst athletes is shown in figure 4.1.

There was no significant difference between the ethnic groups with respect to left ventricular chamber size, either in diastole (black 48.6 ±3.9mm (39-60) vs. white 48.2±3.5mm (40-62); P=0.93), or systole (black 30.8±4.0 (21-44) vs. white 30.5 ±4.7 (20-44); P=0.47). Twenty black athletes (8%) and 12 white athletes (6%) revealed an enlarged (>54mm) left ventricular end-diastolic cavity (P=0.36).

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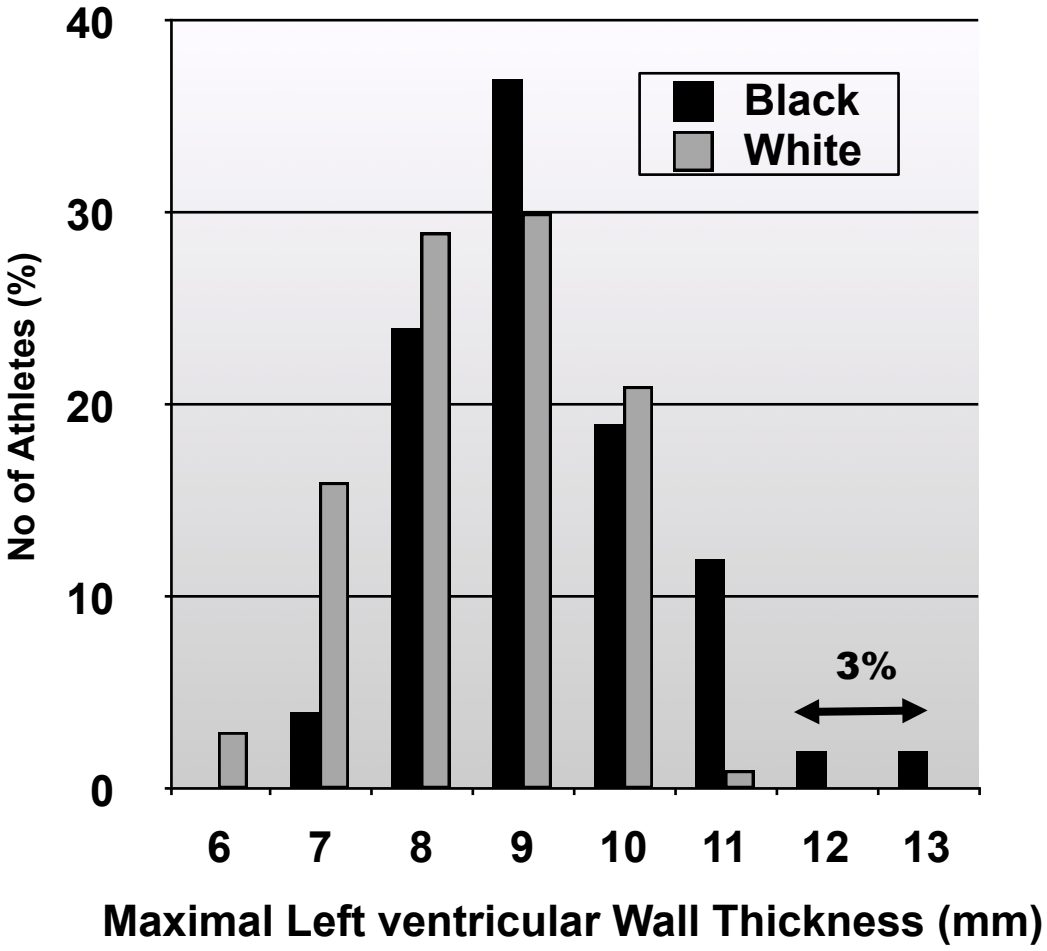
Table 4.4 Comparison of echocardiographic cardiac dimensions between black and white elite female athletes

	BLACK ATHLETES (n=240)	WHITE ATHLETES (n=200)	P VALUE
Ao (mm)	27.2±2.9 (23-38)	26.4±3.5 (17-33)	**0.21**
LA (mm)	35.3±4.7 (21-45)	32.5±2.1 (21-47)	**<0.0001**
LVED (mm)	48.6 ±3.9 (39-60)	48.2±3.5 (40-62)	**0.93**
LVES (mm)	30.8±4.0 (21-44)	30.5 ±4.7 (20-44)	**0.47**
IVSd (mm)	9.0±1.3(6-13)	8.4±1.2 (6-11)	**<0.001**
PTWD (mm)	8.7±1.3(6-12)	8.4±1.2 (6-11)	**0.14**
Max LVWT (mm)	9.2±1.2 (6-13)	8.6±1.2(6-11)	**<0.0001**
LVM (g)	187.2±42 (95-322)	172.3±42 (86-293)	**0.008**
E wave (m/s)	0.89±0.2 (0.6-1.36)	0.90±0.2 (0.53-1.33)	**0.49**
A wave (m/s)	0.41±0.1 (0.2-1.1)	0.44 ±0.1(0.2-0.9)	**0.076**
E/A ratio	2.3±0.8 (1.1-5.5)	2.2±0.8 (1.1-5.5)	**0.15**
E` (m/s)	0.22±0.03 (0.13-0.25)	0.23±0.03 (0.17-0.28)	**0.40**
A` (m/s)	0.07±0.03 (0.02-0.16)	0.06±0.03 (0.03-0.13)	**0.43**
E:E`	4.41±0.71 (2.30-5.61)	4.46±0.74 (1.96-5.55)	**0.39**
EF (%)	67±6.7 (41-78)	66±6.9 (44-76)	**0.48**

Data expressed as mean±standard deviation (limits).

Abbreviations for Table 4.4 - see pages 95/96 (as per table 4.1)

Figure 4.1 Histogram showing the distribution of maximal left ventricular wall thickness in black (black bars) and white (grey bars) female athletes. Three percent of black athletes demonstrated a maximal left ventricular wall thickness of >11mm compared with none of the white athletes



4.2 Left Ventricular Hypertrophy in Female Athletes

The distribution of maximal left ventricular wall thickness is shown in figure 4.1. This passed statistical tests for normal distribution. None of the white athletes or control subjects demonstrated a maximal LVWT of >11mm. In contrast, 8 black athletes (3.3%) exhibited a maximal LVWT >11mm (12-13 mm) and were considered to exhibit LVH. The demographic, echocardiographic and electrocardiographic features of the 8 black athletes with LVH are shown in table 4.5.

The pattern of LVH in all the black female athletes was homogeneous, with a difference of <2mm between adjacent segments. All athletes with left ventricular hypertrophy exhibited a normal LV diastolic cavity size (Table 4.5). None of the athletes with LVH exhibited dynamic left ventricular outflow obstruction.[97]

There were no statistically significant differences in age, weight and BSA between black athletes with left ventricular hypertrophy and those without, respectively (Table 4.5).

All athletes with left ventricular hypertrophy underwent further investigation with an exercise stress test, 48 hour holter monitoring and a cardiac magnetic resonance scan. The results of these investigations will be discussed in chapter 5, section 5.4. However, there was 100% concurrence between echocardiography and cardiac magnetic resonance for the identification of left ventricular hypertrophy across multiple modalities.

Table 4.5 Demographic, Echocardiographic and Electrocardiographic Features of Black Athletes With Left Ventricular Hypertrophy.

Age (yrs)	BSA (m^2)	Sport	LVED (mm)	LVES (mm)	LA (mm)	MLVWT (mm)	LVM (gm)	EF (%)	E (m/s)	A (m/s	E:A	E' m/s)	E:E'	T wave Inv (leads)	LAE	LVH
20	1.62	Judo	53	35	30	12	236	64	1.00	0.47	2.1	0.17	5.9	None	No	No
20	2.01	Netball	48	34	32	12	276	65	0.8	0.4	2	0.15	5.3	None	Yes	No
20	1.82	Sprinting	50	37	36	13	329	66	0.8	0.42	1.90	0.22	3.6	None	No	Yes
21	1.98	Basketball	51	37	36	13	260	68	0.8	0.39	2.1	0.16	5.0	None	No	No
22	1.71	Football	45	26	32	13	279	70	0.9	0.38	2.3	0.19	4.7	V1,V2	No	No
22	2.02	Netball	51	40	37	13	322	65	0.6	0.42	1.4	0.16	3.7	V1,V2	No	No
23	1.87	Football	48	33	31	12	276	67	0.72	0.41	1.8	0.21	3.4	None	No	Yes
24	1.77	Weightlifting	42	24	37	13	211	72	0.91	0.42	2.2	0.21	4.3	None	No	No

Abbreviations for Table 4.5 BSA=body surface area; LA=left atrial diameter; LAE=Voltage criterion for left atrial enlargement; LVED=left ventricular end-diastolic diameter; LVES=left ventricular end-systolic diameter; LVH=voltage criterion for left ventricular hypertrophy; LVM=left ventricular mass; MLVWT=maximal left ventricular wall thickness; T-wave Inv=distribution of T-wave inversions.

4.3 Determinants of left ventricular hypertrophy in athletes

The results of a multivariable linear regression model, assessing the relationship between maximal left ventricular wall thickness and age, BSA, ethnicity and number of hours trained**,** demonstrated that ethnicity was the strongest independent predictor of maximal LVWT (β =0.263 (CI=0.29-0.855; P<0.001)), with age being the only other significant factor (β=-0.155 (CI=-0.07--0.01; P=0.006)). There was no relationship between sporting discipline and LVH.

4.4 Reliability of Left Ventricular Wall Thickness Measurements in Athletes

The averaged coefficients of variance between intra-observer and inter-observer reliability for maximal left ventricular measurements were 4 % and 6.2 % respectively. No attempt was made to re-test, as the the observed variability in measures was low

4.5 Other Cardiac dimensions

The following section describes the impact of ethnicity and sporting participation on the dimensions of other cardiac structures, in particular left atrial diameter and aortic annulus diameter.

4.5.1 Left Atrial Diameter

Black female athletes demonstrated a significant increase in left atrial diameter when compared to black controls (Table 4.3) There were however no significant differences in left atrial diameter between black and white control subjects (Table 4.1), nor between white athletes and white control subjects (Table 4.2). Both distributions passed tests for normality.

Black athletes also exhibited a sigificantly greater left atrial diameter when compared to white athletes. (Table 4.4). The distribution of left atrial diameter is summarised in figure 4.2. Only 2.5% of caucasian athletes had an LA diameter of greater than 40mm, compared with 20.8% of black female athletes ($P<0.001$).

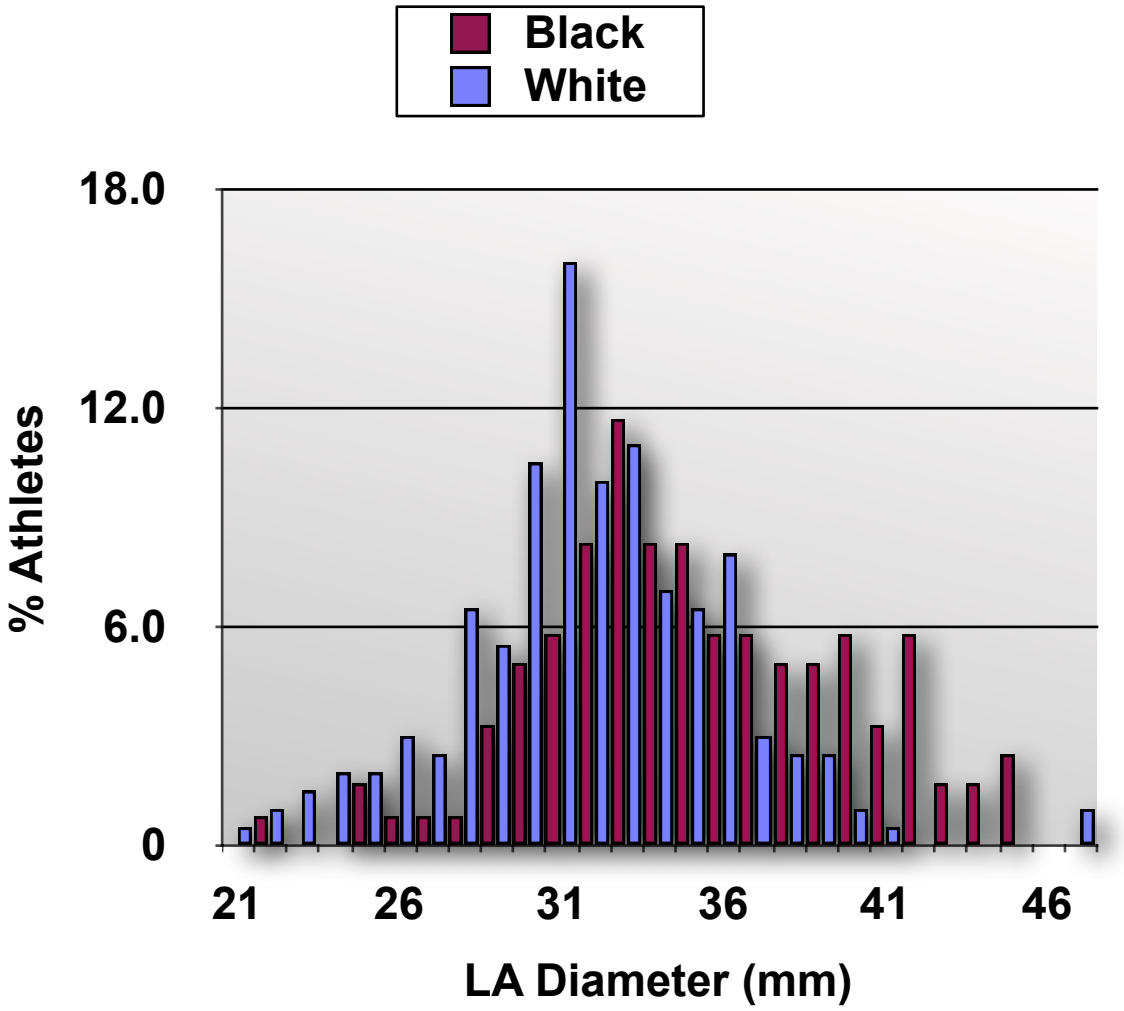


Figure 4.2 Histogram showing distribution of left atrial diameter in female elite black (purple bars) and white (blue bars) athletes. Black athletes had a 9% increase in left atrial diameter when compared to similar white athletes.

4.5.2 Aortic Root Diameter

There was no significant difference in aortic annulus diameter between black and white control subjects (Table 4.1). Both groups of athletes demonstrated a statisically significant increase in aortic annulus diameter when compared to their respective sedentary control subjects (Table 4.2 & Table 4.3). There was however no significant overall difference in annulus diameter between the ethnic groups of athletes. (Table 4.4).

Chapter 5 – The 12-Lead ECG in Elite Black Female Athletes – the Impact of Ethnicity and Regular Physical Activity.

This chapter aims to describe the spectrum of electrocardiographic appearances that may be found in elite black female athletes. Given that all subjects underwent both 12-lead ECG and 2-D trans-thoracic echocardiography; this enables correlation between the two investigations, used most commonly in cardiac screening.

As in chapter 4, comparisons will be made between the two control groups of sedentary subjects, followed by comparison between both groups of athletes with their respective controls and each other. Section 5.1 will examine the baseline ECG findings, with section 5.2 describing the differences the in repolarisation complex between black and white individuals. Following this, the ECG appearances in black and white athletes will be correlated to their trans-thoracic echocardiogram.

5.1 Baseline Electrocardiographic Findings

The following section will describe the baseline ECG findings across the study cohort. The presence

5.1.1 Control Subjects (Table 5.1)

Black control subjects exhibited a small but significant increase in heart rate at rest, when compared to white control subjects (Table 5.1). When compared

to white sedentary controls, Black control subjects had a longer PR interval, with a shorter QRS duration, and QT interval – both uncorrected and corrected (Table 5.1). Black control subjects demonstrated a more leftward axis than white control subjects.(Table 5.1)

Table 5.1 Comparison of electrocardiographic parameters between Black and White female sedentary control subjects.

	BLACK CONTROLS (n=140)	**WHITE CONTROLS (n=140)**	**P VALUE**
Heart rate (bpm)	76 ± 9.5 (56-95)	71 ± 10.9(47-96)	**0.02**
PR interval (ms)	152 ± 20 (116-208)	139 ± 19 (96-198)	**<0.001**
QRS Duration (ms)	83 ± 10 (66-142)	89 ± 9 (60-112)	**<0.001**
QT interval (ms)	367 ± 25 (338-418)	399 ± 27 (332-486)	**<0.001**
QTc (Bazzets) (ms)	403 ± 25 (338-458)	413 ± 20(372-484)	**0.003**
Axis (Degrees)	52 ± 30(-30-108)	60 ± 24 (-22-102)	**0.04**
LAE (%)	4.3	4.3	1.00
RAE(%)	1.4	4.3	0.28
LVH Voltage (%)	8.6	5.7	0.49
Partial RBBB (%)	2.9	8.1	0.11

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate.

Abbreviations for Table 5.1 Bpm=beats per minute; LAE=voltage criterion for left atrial enlargement;QTc=corrected QT interval; RAE=voltage criterion for right atrial enlargement; RBBB=right bundle branch block

There were no significant differences in the incidence of voltage criteria for left atrial hypertrophy, right atrial hypertrophy or left ventricular hypertrophy between the two groups. Partial right bundle branch block was a more common finding amongst white controls, but this failed to reach statistical significance (Table 5.1).

None of the control subjects exhibited pathological Q waves, ST segment depression, left bundle branch block, or epsilon waves.

5.1.2 Black Athletes versus Control Subjects (Table 5.2)

Black athletes exhibited a significantly lower resting heart rate than sedentary black control subjects (Table 5.2). Black athletes also had a small, but significant increase in PR interval. QRS duration was similar between the two groups. There was a significant difference observed in the resting QT interval, but this was not apparent once this had been corrected for heart rate (Table 5.2). Black control subjects also demonstrated a more leftward axis than black athletes (Table 5.2).

Black athletes demonstrated a significantly higher incidence of voltage criteria for left atrial hypertrophy compared with controls. There was however no significant difference in the incidence of voltage criteria for right atrial hypertrophy or left ventricular hypertrophy between the two groups. The prevalence of partial right bundle branch block was significantly higher amongst black athletes compared to controls (Table 5.2).

Table 5.2 Comparison of electrocardiographic parameters between female black athletes and sedentary control subjects.

	BLACK ATHLETES (n=240)	BLACK CONTROLS (n=200)	P VALUE
Heart rate (bpm)	61 ± 8.3 (44-85)	76 ± 9.5 (56-95)	**<0.001**
PR interval (ms)	162 ± 25 (112-246)	152 ± 20 (116-208)	**0.04**
QRS Duration (ms)	84 ± 10 (43-105)	83 ± 10 (66-142)	0.29
QT interval (ms)	400 ± 32 (330-475)	367 ± 25 (338-418)	**<0.001**
QTc (Bazzets) (ms)	404 ± 42 (358- 465)	403 ± 25 (338-458)	0.61
Axis (Degrees)	67 ± 14 (32-89)	52 ± 30(-30-108)	**0.001**
LAE (%)	12.5	4.3	**0.01**
RAE(%)	5	1.4	0.09
LVH Voltage (%)	8	8.6	0.85
Partial RBBB (%)	14	2.9	**<0.001**

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate.

Abbreviations for Table 5.2 Bpm=beats per minute; LAE=voltage criterion for left atrial enlargement;QTc=corrected QT interval; RAE=voltage criterion for right atrial enlargement; RBBB=right bundle branch block

5.1.3 White athletes versus Control Subjects (Table 5.3)

In a similar pattern to that seen in black athletes, white athletes exhibited a significantly lower resting heart rate compared to sedentary white control subjects (Table 5.3). In addition, white athletes demonstrated an increase in

PR interval compared to sedentary control subjects. There were no significant differences in QRS duration, QT interval (both uncorrected and corrected) and QRS axis between athletes and sedentary controls (Table 5.3).

Table 5.3 Comparison of electrocardiographic parameters between female white athletes and sedentary control subjects.

	WHITE ATHLETES (n=200)	WHITE CONTROLS (n=140)	P VALUE
Heart rate (bpm)	60 ± 9.5 (35-85)	71 ± 10.9(47-96)	**<0.0001**
PR interval (ms)	149 ± 23 (88-228)	139 ± 19 (96-198)	**<0.0001**
QRS Duration (ms)	87 ± 10 (66-120)	89 ± 9 (60-112)	0.15
QT interval (ms)	415 ± 33 (290- 447)	399 ± 27 (332-486)	0.09
QTc (Bazzets) (ms)	407 ± 41 (285-474)	413 ± 20(372-484)	0.16
Axis (Degrees)	65 ± 32 (-26-129)	60 ± 24 (-22-102)	0.06
LAE (%)	10	4.3	0.06
RAE(%)	4	4.3	1.0
LVH Voltage (%)	12	5.7	0.059
Partial RBBB (%)	14	8.1	0.086

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate.

Abbreviations for Table 5.3 Bpm=beats per minute; LAE=voltage criterion for left atrial enlargement;QTc=corrected QT interval; RAE=voltage criterion for right atrial enlargement; RBBB=right bundle branch block

Amongst white athletes, voltage criteria for both left atrial and left ventricular hypertrophy, and partial right bundle branch block were a more frequent finding than in sedentary controls. These differences did not however reach statistical significance. There was no difference in the incidence of voltage criteria for right atrial hypertrophy between white athletes and sedentary control subjects (Table 5.3).

5.1.4 Black versus White Athletes (Table 5.4)

Black athletes demonstrated a greater PR interval than white athletes, whereas white athletes revealed a slightly greater QRS duration compared with black athletes (Table 5.4).

There were no significant differences between black athletes and white athletes with respect to QRS axis, QT interval (both uncorrected and corrected), voltage criteria for LVH, right or left atrial hypertrophy or incomplete right bundle branch (Table 5.4).

None of the athletes exhibited pathological Q waves (> 40 msec wide or exceeding in depth 25% of the height of the proceeding R wave), ST segment depression, left bundle branch block, or epsilon waves. The appearances of the repolarisation complex will be considered separately in section 5.2.3.

Table 5.4 - Comparison of electrocardiographic parameters between black and white female elite athletes.

	BLACK ATHLETES (n=240)	WHITE ATHLETES (n=200)	P VALUE
Heart rate (bpm)	61±8.3 (44-85)	60±9.5 (35-85)	**0.26**
PR interval (ms)	162±25 (112-246)	149±23 (88-228)	**<0.001**
QRS Duration (ms)	84±10 (43-105)	87±10 (66-120)	**0.0072**
QT interval (ms)	400±32 (330-475)	415±33 (290- 447)	0.17
QTc (Bazzets) (ms)	404±42 (358- 465)	407±41 (285-474)	0.28
Axis (Degrees)	67±14 (32-89)	65±32 (-26-129)	0.66
LAE (%)	12.5	10	0.45
RAE(%)	5	4	0.65
LVH Voltage (%)	8	12	0.16
Partial RBBB (%)	14	14	0.89

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate.

Abbreviations for Table 5.4 Bpm=beats per minute; LAE=voltage criterion for left atrial enlargement;QTc=corrected QT interval; RAE=voltage criterion for right atrial enlargement; RBBB=right bundle branch block

5.2 Repolarisation Anomalies (Table 5.5)

The repolarisation anomalies that will be considered in the following section will be the presence of J point ST segment elevation or depression and T wave inversions in 2 or more contiguous leads.

5.2.1 Control subjects

Black control subjects exhibited a higher prevalence of T wave inversions than sedentary white subjects, but this difference did not reach statistical significance. (Table 5.5)

Amongst black control subjects, T wave inversions were distributed equally across both the inferior (n=6) and anterior leads (n=6). This differed slightly from the distribution pattern observed in white controls, with T wave inversions being predominately seen in the inferior leads (n=4, 67%) rather than the anterior leads (n=2, 33%). In no control subject (black or white) did the maximum T wave voltage exceed -0.2mV – i.e. “deep” T wave inversions.

In total, 10 black sedentary control subjects (7.1%) and 12 (8.5%) white sedentary control subjects demonstrated J point ST segment elevation (P=0.82). In all subjects this was confined to the anterior pre-cordial leads – i.e. leads V1-V4.

5.2.2. Athletes versus Control subjects

When compared to sedentary black controls, black athletes exhibited a higher prevalence of J point ST segment elevation than black sedentary control subjects - but this did not reach statistical significance(Table 5.5). In contrast, white control subjects demonstrated a significantly higher prevalence of J point ST segment elevation when compared to white athletes (White controls n=12 (8.5%) vs. white athletes n=2 (1%); P<0.001). Amongst all female athletes and control subjects, ST elevation was confined to the anterior pre-cordial leads (V1-V4).

Table 5.5 Prevalence of repolarisation anomalies amongst Female athletes and control subjects

	Black Controls	Black Athletes	White Controls	White Athletes	P Value
ST elev (N=, %)	10 (7.1%)	26 (11%)	12 (8.5%)	2 (1%)	<0.001[a,b]
T-wave Inv (N=, %)	12 (8.5%)	34(14%)	6 (4.3%)	9 (4.5%)	<0.001[a]

[a] Statistically significant between black athletes and white athletes

[b] Statistically significant between white athletes and white controls

Black athletes demonstrated a higher prevalence of contiguous T wave inversions when compared to sedentary black control subjects. However, this failed to reach statistical significance (Table 5.5; P=0.14). There was no difference observed in the prevalence of contiguous T wave inversions between white athletes and white control subjects (Table 5.5).

5.2.3 Black versus white athletes

Black athletes demonstrated a higher prevalence of ST segment elevation compared with white athletes (Table 5.5). Black athletes also exhibited a higher prevalence of contiguous T wave inversions compared with white athletes (Table 5.5; Figure 5.1). In black athletes T wave inversions were confined to leads V1-V3 and exceeded -0.2 mV (deep T wave inversions) in 6 (2.5%) individuals (Figure 5.2; C). In contrast, white athletes only showed T wave inversions in leads III and aVF (i.e. in the inferior leads) and none exhibited deep T wave inversions.

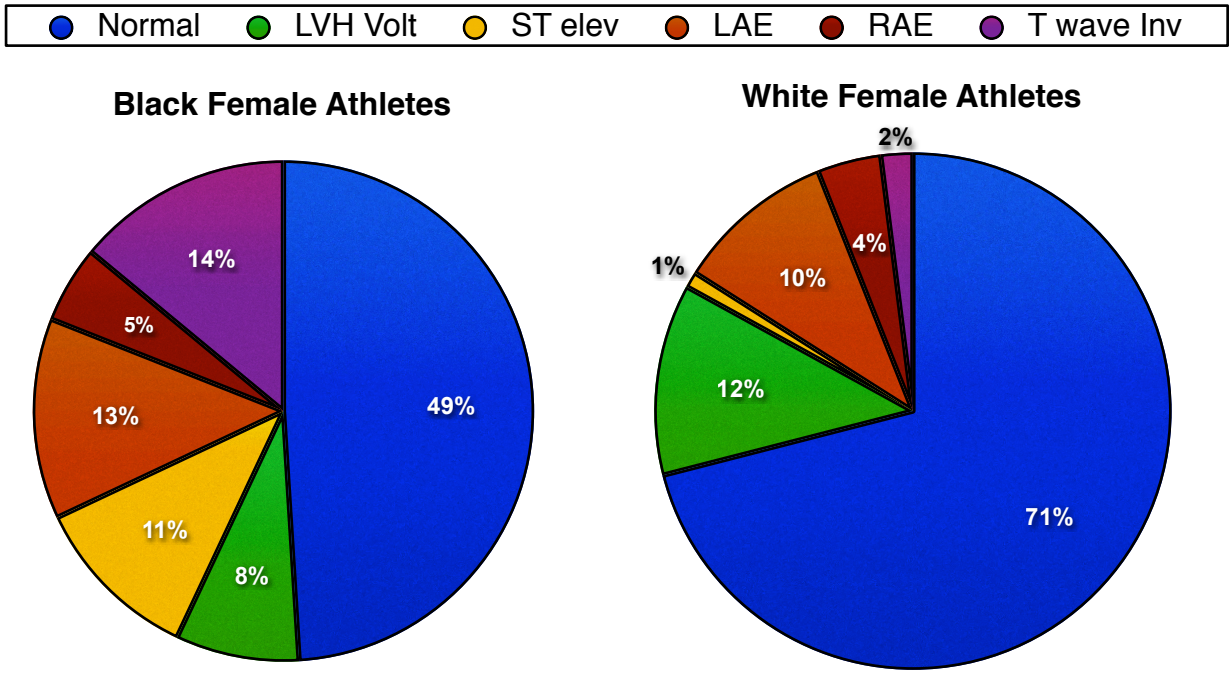


Figure 5.1 Pie charts comparing ECG anomalies in black and white athletes. Black athletes exhibited a higher prevalence of ST segment elevation and T wave inversions than white athletes. Abbreviations – LVH Volt – Voltage criteria for Left Ventricular Hypertrophy, LAE – Voltage criteria for left atrial enlargement, RAE – Voltage criteria for right atrial enlargement, ST Elev – ST segment elevation, T wave inv – Significant T-wave inversions.

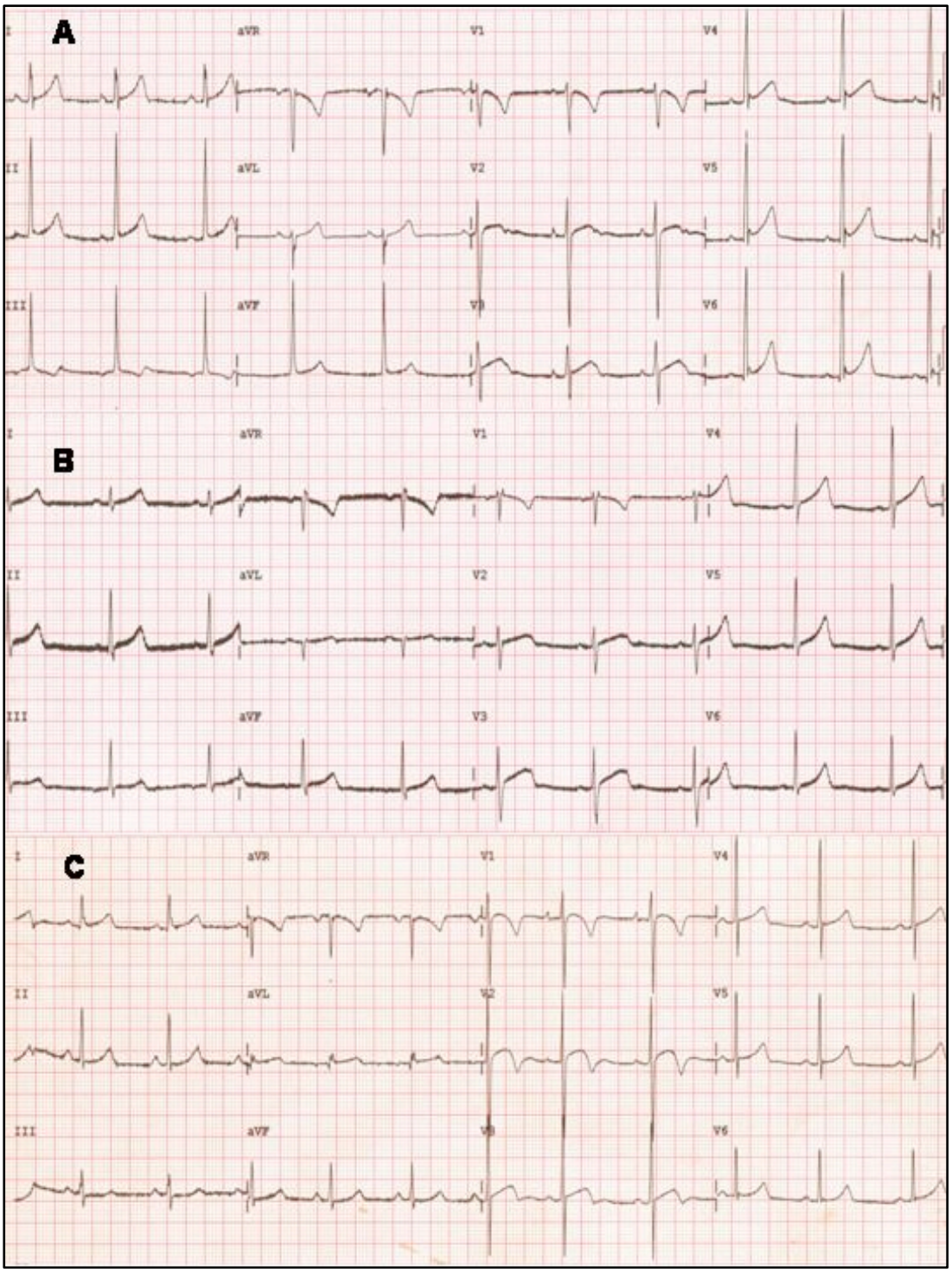


Figure 5.2 – Spectra of ECG observations in black female athletes revealing Sokolow-Lyon voltage criteria for LVH and elevated J point in the lateral leads (A), partial right bundle branch block with accompanying convex ST elevation in leads V_1 through V_3 (B), and convex ST-segment elevation and deep T-wave inversions in leads V_1 through V_3.

5.2.4 Determinants of Repolarisation Anomalies

The results of a binary logistic regression model, with the dependant variable being the presence of T wave inversions, demonstrated that black ethnicity was the only significant independent predictive factor (β=1.94, S.E.=0.417; P=0.003). This means that a black female athlete is approximately 7 times more likely to exhibit T wave inversions than a similar white athlete. Black ethnicity was also the strongest independent predictive factor (β=1.29, S.E. =349; p<0.001) when ST segment elevation was used as a dependent variable in the model. This equates to a 3.5 times chance of a black athlete having significant ST elevation if compared to a white athlete. In addition, athlete height in both races having a weak additional effect (β=0.042, S.E.=0.021; P=0.043).

5.3 Correlation between ECG and Echocardiogram

There was a weak correlation between the presence of T wave inversions and magnitude of LVWT and LVM in both groups of athletes (maximal LVWT; P=0.039, LVM; P=0.041). However, there were no significant differences in absolute values of maximal LVWT between any athletes or controls with T wave inversions and those without (black controls; P=0.76, black athletes; P=0.12, white controls; P=0.78, white athletes; P=0.07). The identification of T wave inversions did not predict the presence of LVH or increased LV cavity size. There was no relationship between the presence of Sokolow-Lyon voltage criteria for LVH on the ECG and maximal LVWT or LVM (maximal LVWT; P=0.278, LVM; P=0.408).

5.4 Subsequent investigations

All athletes or controls who exhibited echocardiographic left ventricular hypertrophy and/or deep T wave inversions were referred for further investigations, as detailed in chapter 2, section 2.3. All athletes that were identified with either of the above findings underwent the full compliment of investigations.

Twelve black athletes underwent an exercise stress test, 48 hour Holter monitoring and a CMR scan. None of the 12 athletes demonstrated any phenotypic features of HCM or any other form of cardiomyopathy. Specifically, none of the 12 athletes exhibited flat BP responses to exercise,[93] or >1000 ventricular extra-systoles/non-sustained ventricular tachycardia[94] or late gadolinium enhancement (to indicate myocardial fibrosis),[98] apical hypertrophy[98] and right ventricular wall motion abnormalities,[99] on exercise testing, 48-hour Holter monitor and the CMR scan respectively. There was 100% concurrence between echocardiography and CMR for the identification of left ventricular hypertrophy in all black athletes with echocardiographic LVH.

None of the white athletes or control subjects demonstrated echocardiographic or ECG findings that necessitated further investigations.

Chapter 6 - The Significance of Repolarisation Anomalies in Black Male Athletes

The following section, will attempt to describe the significance of the repolarisation anomalies that have previously been reported in cohorts of black male athletes.[18,19,53,54] As described in chapter 2, a large cohort of black and white male athletes were studied using both ECG and echocardiography and compared to a cohort of black male control subjects and a cohort of black patients with hypertrophic cardiomyopathy that underwent a similar series of investigations.

The ECG and echocardiographic appearances in the male athletes will be described first, followed by the control group, and finally the cohort with hypertrophic cardiomyopathy. Comparisons will be made between the athlete cohort, the control cohort and the hypertrophic cardiomyopathy group. Finally, this chapter will report the results on the longitudinal follow-up of the athlete cohort and in doing so, assess the significance of the ECG and echocardiographic appearances observed.

6.1 The 12-Lead ECG In Male Subjects

6.1.1 Baseline Electrocardiographic findings

The baseline ECG findings across the cohort of healthy individuals are described below, followed by the individuals with hypertrophic cardiomyopathy.

6.1.1.1 Baseline ECG findings in Healthy Male Subjects (Table 6.1)

White athletes had a lower resting heart rate when compared to black athletes, with a greater proportion exhibiting significant sinus bradycardia, (HR <60bpm)(Table 6.1). Black athletes however had a longer PR interval at rest (168 ms Vs. 156 ms; $p<0.001$), and a significantly higher prevalence of first degree heart block when compared to white male athletes (Table 6.10. There were also small, but statistically significant, differences in QRS duration and corrected QT interval between black and white athletes (Table 6.1).

The incidence of partial right bundle branch block (RBBB) was significantly higher in black athletes , but complete RBBB was more commonly observed amongst white healthy individuals. The overall incidence of full RBBB was however low in both groups (Table 6.1).

When compared to black sedentary control subjects, black male athletes had a significantly lower resting heart rate. Only 20% of black sedentary individuals had a resting sinus bradycardia compared to over 60% of black athletes. Similarly, the resting PR interval and the incidence of first incidence of first degree heart block was significantly greater amongst black athletes.

With respect to voltage criteria for cardiac chamber enlargement, electrocardiographic left ventricular hypertrophy was seen less frequently in black athletes than in either white athletes or black sedentary control

subjects (Table 6.1). In contrast, left and right atrial enlargement was observed significantly more frequently amongst black athletes than in white athletes or sedentary controls.

Table 6.1 Electrocardiographic characteristics in healthy male subjects: Black athletes, white athletes and sedentary black controls.

Parameter	Black Athletes (n=904;%)	White Athletes (n=1819;%)	Black Controls (n=119;%)	P Value: BAs vs. WA	P-Value: BAs v. BC
Sinus bradycardia	47.1	60.7	20.2	**<0.001**	**<0.001**
PR interval (ms)	168 ±28	156 ± 27	153 ±19	**<0.001**	**<0.001**
1º AV Block	11.2	3.6	2.5	**<0.001**	**0.003**
QRS Duration (ms)	88 ± 13	96±10	89 ± 9	**<0.001**	0.42
QTc (ms)	393 ± 26	404 ± 20	400 ± 18	**<0.001**	**0.005**
Partial RBBB	24.7	12.3	5.00	**<0.001**	**<0.001**
RBBB	0.3	1.2	0	**0.03**	0.53
Left-axis deviation	1.1	0.6	2.5	0.10	0.20
Right-axis deviation	0.1	0.9	0	**0.01**	0.72
Pathological Q-waves	0.9	0.4	0	0.152	0.31
LA enlargement	8.6	2.8	5.9	**<0.001**	0.17
RA enlargement	6.3	0.3	2.5	**<0.001**	0.066
LVH	23.2	36.8	39.5	**<0.001**	**<0.001**
RVH	13.3	2.6	4.2	**<0.001**	**<0.001**
Inverted T waves	22.8	3.7	10.1	**<0.001**	**0.003**
T-wave inversions in V1-V4	12.7	1.9	4.2	**<0.001**	**0.007**
T-wave inversions inferior leads	6	1.5	2.5	**<0.001**	0.12
T-wave inversions in lateral leads	4.1	0.3	3.4	**<0.001**	0.70
Deep T-wave inversions	12.1	1	1.7	**<0.001**	**0.002**
ST-segment elevation	63.2	26.5	65.5	**<0.001**	0.61
ST-segment depression	0.4	0	0	**0.01**	0.47

Data expressed as mean±standard deviation (limits) or percentages (%), as appropriate. **Abbreviations - See Page 125**

Abbreviations for Table 6.1 AV - atrio-ventricular node, LA enlargement - Voltage criteria for left atrial enlargement, LVH - Voltage criteria for left ventricular hypertrophy, QTc - Corrected QT interval, RA enlargement - Right atrial Voltage criteria for right atrial enlargement, RBBB - right bundle branch block, RVH - Voltage criteria for right ventricular hypertrophy.

6.1.1.2. Baseline ECG findings in Subjects with HCM

The baseline ECG characteristics in the cohort of patients with HCM are summarized in table 6.2. No attempt has been made to compared baseline ECG intervals between the cohorts due to the use of medications in the HCM cohort that affect heart rate and myocardial function, altering these parameters and making comparison invalid.

With respect to voltage criteria for chamber enlargement, both left ventricular hypertrophy and left atrial enlargement were observed significantly more frequently amongst the individuals with HCM that in either groups of athletes or control subjects (LVH HCM 53.8% vs. BA 23.2% vs. WA 36.9% vs. BC 39.5%; $P<0.001$). Pathological Q waves and left axis deviation were also observed significantly more frequently in the HCM cohort, compared to both the athlete and controls groups. The appearance of the repolarisation complexes will be considered in section 6.1.2

Table 6.2 Electrocardiographic characteristics in patients with HCM.

ECG Characteristics	% Patients
LVH (Sokolow and Lyon)	53.8
LA enlargement	44.2
Pathological Q waves	11.5
Left-axis deviation	11.5
Inverted T-waves	82.7
T-wave inversions leads V1-V4	3.8
T-wave inversions in inferior leads	1.9
T-wave inversions in lateral leads	76.9
Deep T wave inversions	69.2
ST segment elevation	9.6
ST segment Depression	50

Data expressed as % of total cohort

Abbreviations for Table 6.2 - LA enlargement - left atrial enlargement, LVH - Voltage criteria for left ventricular hypertrophy.

6.1.2 Repolarisation changes - Prevalence and Distribution

In the following section, the aim is to describe the prevalence and distribution of anomalies affecting the repolarisation phase and the ST segment of the ECG complex. Firstly, racial differences between the black and white athlete groups will be considered, before comparing the black athletic group individually with black sedentary controls and black individuals with HCM.

6.1.2.1 Black Male Athletes vs. White Male athletes

Both ST segment elevation and T-wave inversions were observed more frequently in black male athletes than in white athletes (Table 6.1). T wave inversions, including deep T-wave inversions, were present in 22.8% of black athletes compared to 3.7% of white athletes.

T-wave inversions amongst black athletes were predominately observed in the anterior leads (12.7%; Figure 6.1A, Figure 6.2). T wave inversions in the lateral leads were observed significantly less frequently, with only 4.1% of black athletes demonstrating such changes.

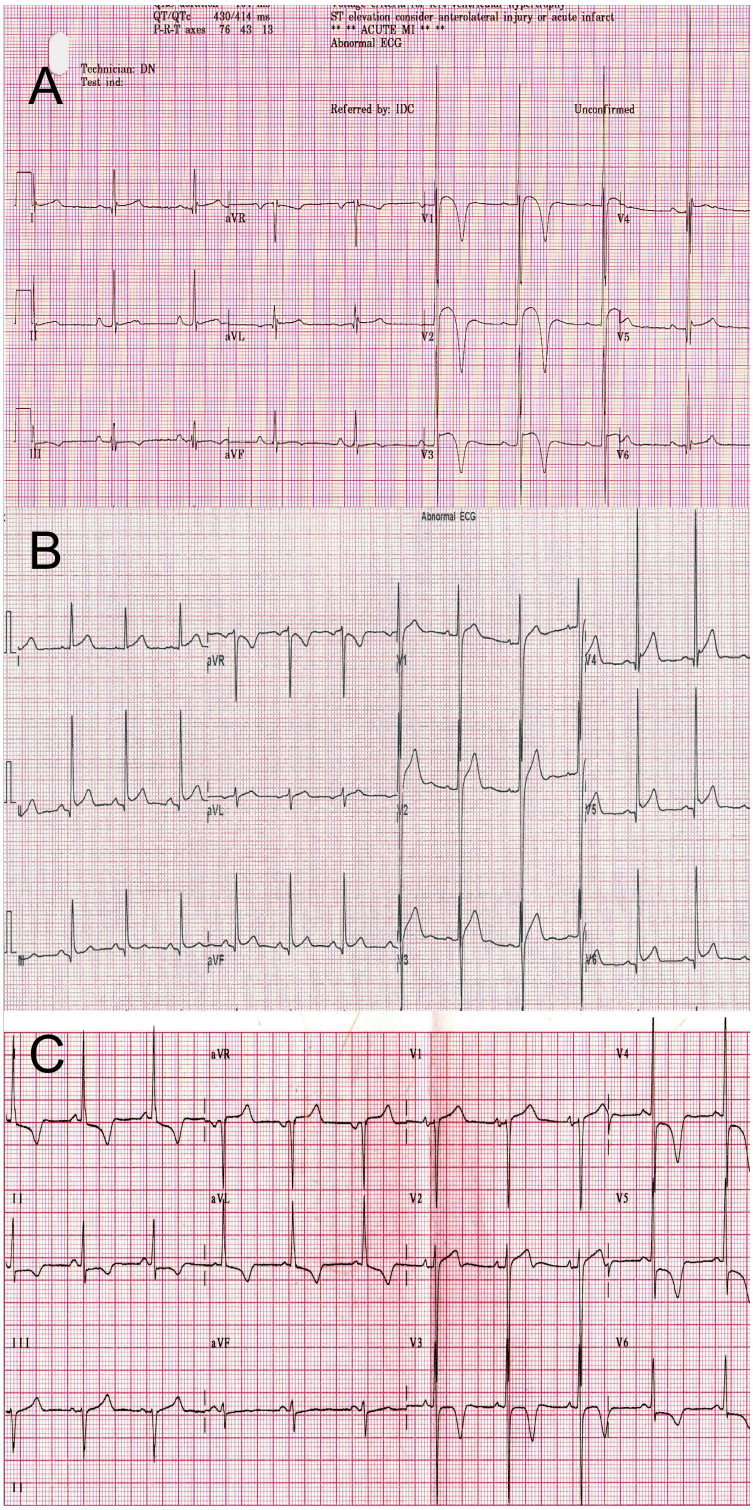
ST segment depression was rare in both groups, being absent amongst white athletes, and seen in just 0.4% of black athletes. ST segment elevation was observed more frequently amongst black male athletes than in white athletes.

6.1.2.2 Black Male athletes vs. black sedentary controls vs. black HCM patients

There were no differences in the prevalence of ST segment elevation between black athletes and black sedentary controls. However, ST segment elevation was observed significantly more frequently in healthy individuals than in individuals with hypertrophic cardiomyopathy (BAs 63.2% vs. BC 65.5% vs. HCM 9.6%, $P<0.001$)(Figure 6.2A). In contrast, ST segment depression was virtually absent in athletes and controls, but

was common amongst individuals with HCM (BAs 0.4% vs. BCs 0% HCM 50%, Figure 6.1C).

Figure 6.1 A series of ECGs demonstrating typical repolaristation changes in black male individuals.



(A) Black long distance runner with convex ST segment elevation and deep T wave inversions in leads V1-V3,

(B) Black sedentary individual with widespread ST-segement elevation of the concave /saddle shaped and hight take off pattern,

(C) Black hypertrophic cardiomyopathy patient with ST-segment depression and deep T wave inversions in the lateral leads.

Individuals with HCM exhibited a significantly higher prevalence of T wave inversions (including deep T-wave inversions) compared with athletes and controls (BAs 22.8% vs. BCs 10.1% vs. HCM 82.7%; P<0.001; Figure 6.2A). With respect to the distribution of T-wave inversions, amongst black athletes these were observed significantly more frequently in the anterior chest leads when compared to both black control subjects and black patients with hypertrophic cardiomyopathy (BAs 12.7% vs. BCs 4.2% vs. HCM 3.8%; P=0.006; Figure 6.2B). In contrast, black patients with HCM had a significantly higher prevalence of T wave inversions in the lateral leads (BAs 4.1% vs. BCs 3.4% vs. HCM 76.9%; P<0.001; Figure 6.2B). all groups exhibited a similar prevalence of T wave inversion in the inferior leads (BAs 6% vs. BCs 2.5% vs. HCM 1.9%; P=0.21; Figure 6.2B).

6.1.3 ST-segment morphology

A variety of ST segment morphologies were noted amongst black athletes. These included convex ST-segments, concave/saddle-shaped and high take off patterns (figure 6.3). The concave ST-segment pattern was more prevalent in black athletes than in black control subjects and white athletes (BAs 38.4% vs. BCs 6.7% vs. WAs 2.7%; P<0.001). Of note, the majority (64.3%) of T wave inversions across the anterior leads in black athletes were preceded by a pattern of convex ST segment elevation.

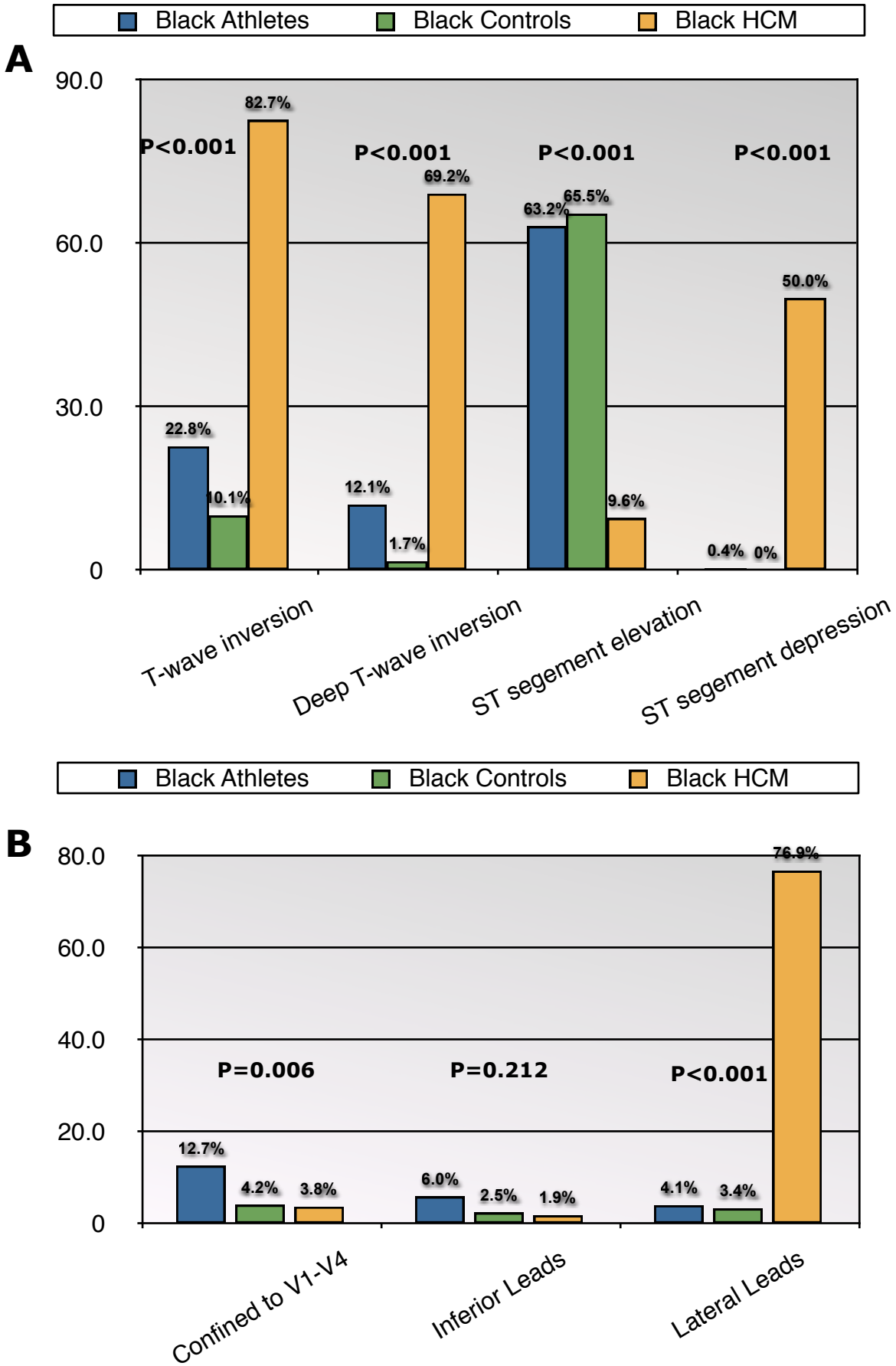


Figure 6.2: (A) Histogram demonstrating the prevalence of repolarisation changes as a percentage (%) of the total cohort in black athletes, black controls and black patients with Hypertrophic Cardiomyopathy. (B) Histogram demonstrating the distribution of T-wave inversions as percentage (%) of the total cohort in the three groups.

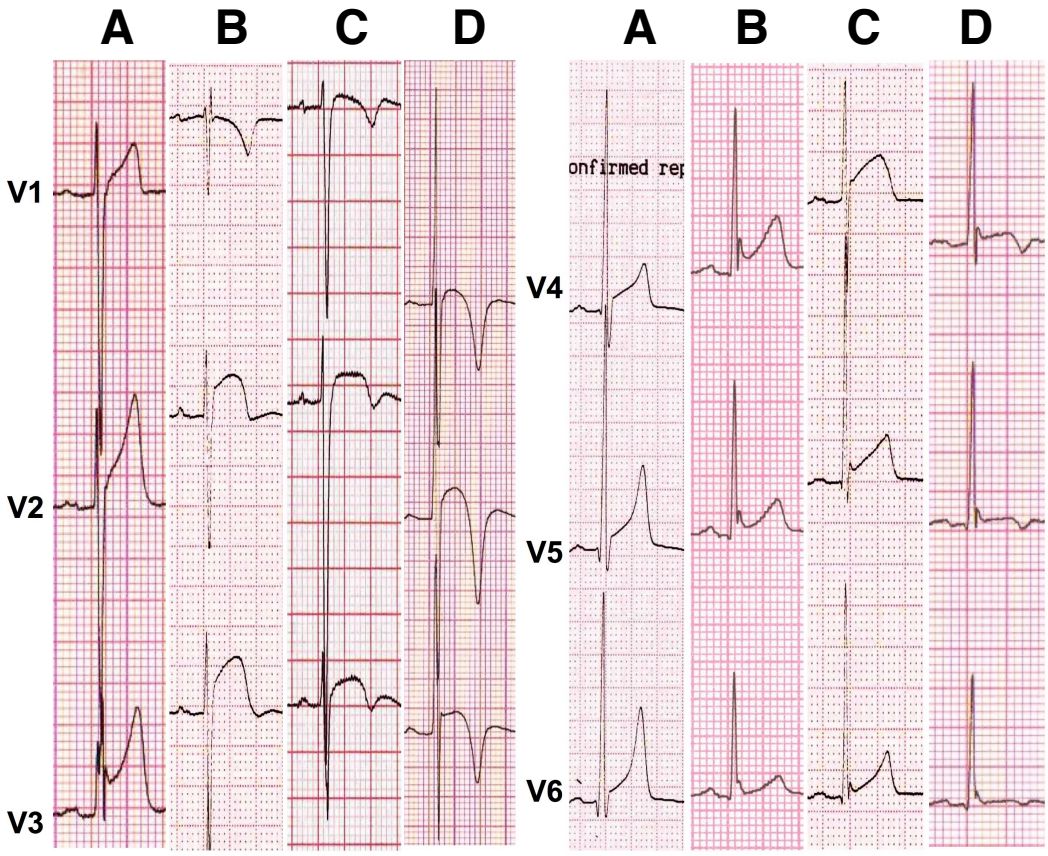


Figure 6.3 - Examples of common ECG ST-segment morphologies in leads V1-3 & V4-6 amongst black athletes **(A)** - Concave J point ST elevation with a “high take off” pattern, **(B)** Convex Dome shaped ST-elevation, **(C)** Convex ST elevation associated with T wave inversions in leads V1-3, **(D)** Deep T wave inversions extending from V1-V5, assoicated with convex ST segment elvation

6.2 The Echocardiographic Appearance in Male Subjects (Table 6.3/ Table 6.4)

6.2.1 Athletes vs. Controls (Table 6.3)

With respect to measures of left ventricular size, both cohorts of athletes exhibited greater maximal LVWT and LV diastolic cavity diameter when compared to the sedentary black male control subjects. (Table 6.3). In addition, estimates of left ventricular mass were also significantly greater in the athletic groups, compared to sedentary controls.

Transverse left atrial diameter was also greater in the athletic groups compared to sedentary controls, as was aortic root diameter. There was a small, but statistically significant difference in measures of early diastolic filling velocity (e-wave) across the mitral valve, between the black athletes and the black control subjects, but this difference was not seen in the white athlete group. All athletes and control subjects exhibited normal measures of both systolic and diastolic function.

Table 6.3 Comparison of standard echocardiographic parameters in male black athletes, male white athletes and male control subjects.

	Black Athletes (n=904)	White Athletes (n=1819)	Black Controls (n=119)	P Value
Ao (mm)	30.2 ± 3.3 (22-39)	29.5 ±3.3 (21-40)	28.2 ± 3.1 (22-35)	<0.001[a,b,c]
LA (mm)	35.4 ± 4.5 (27-45)	34.7 ± 4.7 (25-44)	33.0 ± 4.8 (24-42)	0.002[a,b]
LVED (mm)	52.6 ± 4.4 (35-60)	52.6 ± 4.3 (34-60)	47.9 ± 3.4 (32-55)	<0.001[b,c]
Max LVWT (mm)	10.6 ± 1.6 (6-16)	10.0 ± 1.2 (6-13)	9.2 ± 1.4 (6-11)	<0.001[a,b,c]
LVM (g)	203 ± 50.6 (90-340)	188.3 ± 44.1 (85-320)	155.2 ± 34.9 (80-280)	<0.001[a,b,c]
LVM/BSA (g/m^2)	103.7 ± 25.1	98.5 ± 21.8	84.0 ±14.8	<0.001[a,b,c]
E-wave (m/s)	0.8 ± 0.2 (0.5-1.8)	0.9 ± 0.2 (0.5-1.9)	0.9 ± 0.2 (0.4-1.7)	<0.001[a,b]
A-Wave (m/s)	0.5 ± 0.2 (0.2 - 0.9)	0.4 ± 0.1 (0.2 - 0.9)	0.5 ± 0.1 (0.2-0.8)	0.34
E/A	2.1 ± 0.9	2.2 ± 0.8	2.2 ± 0.6	0.004[a]

[a]Statistically significant between black male athletes and white male athletes
[b]Statistically significant between black male athletes and black male controls
[c]Statistically significant between white male athletes and black controls

Abbreviations - A wave - late diastolic mitral valve inflow peak velocity, Ao - Aortic annulus diameter, BSA – Body Surface Area, E wave - early diastolic mitral valve peak inflow velocity, E:A – ratio of peak early diastolic mitral inflow velocity to peak late diastole mitral inflow velocity, LVED - maximal left ventricular cavity dimension in end-diastole, LVM - left ventricular mass, Max LVWT - maximal left ventricular wall thickness in end-diastole

6.2.2 Black vs. White Male athletes (Table 6.3)

Overall, black male athletes demonstrated an significantly greater maximal left ventricular wall thickness when compared to white athletes. With respect to absolute measures, 112 (12.4%) of black athletes exhibited echocardiographic LVH, i.e. a maximal left ventricular wall thickness of >12mm. This compared to only 29 (1.6%) of white athletes. In no athlete did the maximal observed LVWT exceed 16mm (figure 6.4).

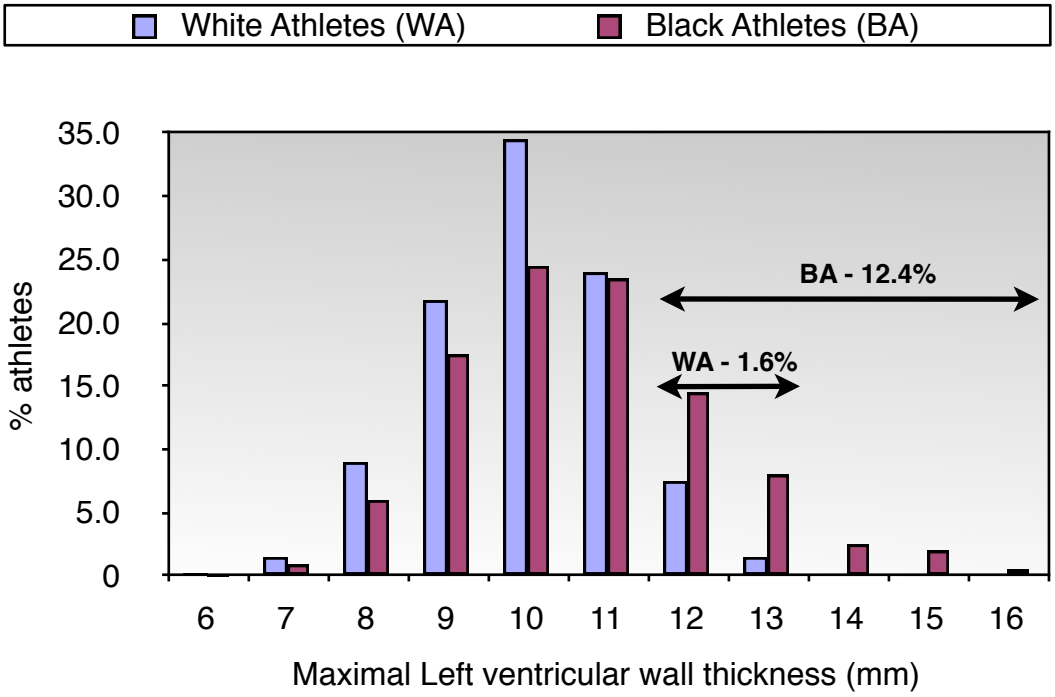


Figure 6.4 Histogram demonstrating the distribution of maximal left ventriuclar wall thickness at end-diastole as a percentage of the total black athlete (Pink bars) and white athlete (Purple bars) cohort, respectively. 12.4% of black athletes had a left ventricular hypertrophy vs. 1.6% of white athletes (Incidcated by black arrows)

All athletes with left ventricular hypertrophy had correspondingly normal or mild dilatation of the left ventricular cavity, along with normal indices of both systolic and diastolic function. In no athlete did the difference between the septal and posterior left ventricular wall thickness differ by more than 1mm.

6.2.3 The Echocardiogram in black patients with Hypertrophic Cardiomyopathy (Table 6.4).

Overall, the echocardiographic appearances of the cohort of patients with HCM was consistent with the clinical phenotype. Almost all (98.1%) of patients with HCM exhibited echocardiographic left ventricular hypertrophy, associated with a non dilated left ventricular cavity, left atrial enlargement and impairment of diastolic function. Systolic anterior motion of the mitral valve (SAM) was observed in in 23.1%, all of which demonstrated an associated left ventricular outflow tract gradient of greater than 30mmHg at rest.

6.3 Further Testing

All 350 athletes with T-wave inversions and/or left ventricular hypertrophy on echocardiography were invited to undergo further investigations to exclude the broader phenotype of HCM. These investigations are described in chapter 2, section 3, and include exercise stress testing (including measures of cardiopulmonary function), Holter monitor recording, cardiac magnetic resonance imaging and a comprehensive family evaluation.

Table 6.4 The Echocardiographic characteristics of black patients with HCM

	Black HCM patients (n = 52)
Ao (mm)	31.3 ± 3.7
LA (mm)	40.9 ± 7.3
LVED (mm)	44.0 ± 6.1
Max LVWT (mm)	17.4 ± 4.9
LVM (g)	279.6 ± 106.5
E-wave (m/s)	0.70 ± 0.18
A-Wave (m/s)	0.67 ± 0.18
E/A	1.11 ± 0.44
SAM (%)	23.1
LVOT Gradient >30mmHg (resting, %)	23.1
LVH Pattern (%)	
ASH	25
Concentric	44.2
Apical	28.8
No Hypertrophy	1.9

Abbreviations - A wave - late diastolic mitral valve inflow peak velocity, Ao - Aortic annulus diameter, E wave - early diastolic mitral valve peak inflow velocity, E:A – ratio of peak early diastolic mitral inflow velocity to peak late diastole mitral inflow velocity, LVED - maximal left ventricular cavity dimension in end-diastole, LVM - left ventricular mass, Max LVWT - maximal left ventricular wall thickness in end-diastole, LVOT - Left ventricular outflow tract, SAM - systolic anterior motion of the mitral valve.

Of the 350 athletes, 233 (66%) underwent the full complement of investigations that were offered. The remaining 34% either failed to attend clinic appointments (n=62, 18%), attended only for some of the investigations (n=20, 6%), or moved clubs and could not be traced (n=35, 10%).

6.3.1 Further Testing Results

All athletes achieved a peak-VO2 of greater than 120% predicted. Thirteen athletes exhibited ≥ 100 ventricular or supra-ventricular extrasystoles over 24 hours. In no subject did this exceed 0.5% of the total number of heart beats.

One black athlete exhibited asymmetric septal hypertrophy (15mm) on cardiac magnetic resonance imaging, that was not apparent on trans thoracic echocardiography. There was no evidence of late gadolinium enhancement in any subject studied that would be indicative of myocardial fibrosis.

First degree relatives were investigated in only 33 (9.4%) athletes. Phenotypic evidence of hypertrophic cardiomyopathy was identified in one parent. This case will be discussed in further detail in section 6.4..

6.4 Determinants of repolarisation changes in athletes

Univariate analyses demonstrated a significant association between ST segment elevation and ethnicity, age, body surface area, hours of training per week, left atrial size and maximum left ventricular wall thickness. Multivariable analysis revealed that black ethnicity was the strongest independent predictor with black athletes being four times more likely to exhibit ST segment elevation compared with white athletes (OR 3.95; 95% CI 2.73-5.75, P<0.001). The only other significant predictor of ST segment elevation was the number of hours trained per week (OR 1.03; 95% CI 1.00-1.06; P=0.03).

With respect to T wave inversions, univariate analysis demonstrated a significant association between T wave inversions and ethnicity, age, hours of training per week, systolic blood pressure and maximum left ventricular wall thickness. After adjustment for all variables, black ethnicity was the strongest independent predictor. Overall, black athletes were almost six times more likely to exhibit T-wave inversions compared to white athletes (OR 5.56; 95% CI 3.55-8.70; P<0.001). The single other predictor identified was maximum left ventricular wall thickness (OR 1.18; 95% CI 1.02-1.35; P=0.02).

6.5 Clinical Significance of Repolarisation Changes

In total, 2723 athletes underwent cardiac evaluation as part of this study cohort. Of these, follow up data was available in 1243 athletes who underwent ≥ 2 evaluations either as part of the standard pre-participation screening programme, or as a result of on-going clinical surveillance due to the presence of marked repolarisation changes and/or LVH. During the mean follow-up period of 69.7 ± 29.6 months, three athletes were diagnosed with hypertrophic cardiomyopathy. Their ECG and echocardiographic findings are summarised in figure 6.5.

Athlete 1, a black soccer player was diagnosed following investigations for an abnormal ECG. This showed deep T-wave inversions and ST-segment depression in the inferior and lateral leads (Figure 6.5A). Subsequent trans-thoracic echocardiography demonstrated asymmetric left ventricular hypertrophy, with a maximal septal wall thickness of 15mm, and a non dilated left ventricular cavity. This was subsequently confirmed on cardiac magnetic resonance scanning.

Athlete 2, also a black soccer player, was diagnosed retrospectively having been successfully resuscitated from ventricular fibrillation during a football match. His initial screening ECG had shown T wave inversions in the inferior and lateral leads (Figure 6.5B), which was followed by trans thoracic echocardiogram that demonstrated mild concentric LVH with a non-dilated left ventricular cavity, a finding confirmed on cardiac magnetic resonance imaging. The features were initially considered to represent

athletes heart, based on a peak VO2 max >120% of maximum predicted and the absence of the broader HCM phenotype. Subsequent events did however confirm the diagnosis of HCM, rather than cardiac athletic adaptation.

Athlete	LA	IVSd	LVPWd	LVED	LVM	E/A
1	42	15	12	48	302	1.83
2	36	14	14	46	255	2.39
3	34	11	9	49	175	2.4

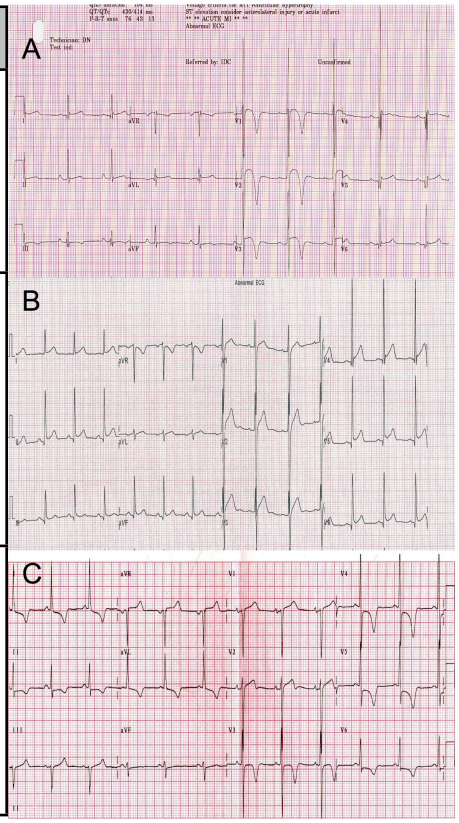


Figure 6.5 - 12 Lead Electrocardiograms and echocardiographic data of all three athletes diagnosed with hypertrophic cardiomyopathy.

Abbreviations for figure 6.5 A- late diastolic mitral valve inflow peak velocity; E - early diastolic mitral valve inflow peak velocity; IVSd - maximal left ventricular septal wall thickness at end diastole; LA - left atrium; LVED - left ventricular cavity diameter in end-diastole; LVM - left ventricular mass; LVPWd - left ventricular posterior wall thickness in end-diastole.

Athlete 3, a caucasian triathlete, also exhibited T wave inversions in the inferior and lateral leads (Figure 6.5C), but subsequent trans-thoracic echocardiography and cardiac magnetic resonance scanning

demonstrated a structurally normal heart. The athlete also had a high peak VO2 and a normal Holter monitor recording. The diagnosis of HCM was reached after the identification of an apical form HCM in his mother followed by subsequent conformation of a myosin-binding protein C mutation in both individuals.

6.6 Other Significant findings in Male Athletes

In addition to the three athletes diagnosed with hypertrophic cardiomyopathy, an incidence of 1 in 908, nineteen further athletes exhibited cardiac electrical or structural abnormalities. These are listed in table 6.5.

Cardiac Abnormality	N=
Electrical	
Wolff-Parkinson-White	4
Long QT syndrome	3
Brugada Syndrome	1
Structural	
Bicuspid Aortic Valve	3
Patent Foramen Ovale	3
Atrial Septal Defect	2
Ventricular Septal Defect	1
Mitral Valve Prolapse	1
Cor-triatritrum	1

Table 6.5 - Other cardiac abnormalities identified at routine pre-participation screening amongst this cohort of healthy individuals.

Chapter 7 – Discussion

7.1 Introduction

Numbers of black athletes that compete at a local, national and international level have been steadily increasing since the 1960's. Initially this rise in participation was confined to male athletes – but since the mid 1980's female black athletes have emerged to dominate certain sporting arenas. Numbers of female black athletes are predicted to continue increase over the coming decades, and sporting organisations have begun to specifically target this demographic group.[82]

In parallel to the increase the numbers of black participants, both male and female, in elite sport, governing bodies[15], organisers of international sporting competitions[14] and cardiac societies on both sides of the Atlantic[17,77], have advocated the adoption of pre-participation cardiac screening with a 12-lead ECG and subsequent trans-thoracic echocardiography. The aim of these programmes has been the reduction in numbers of sudden cardiac death during sporting activity, as is discussed in Chapter 1, section 1.5.

The criteria used to derive the normal range of electrocardiographic and echocardiographic parameters in athletes have been derived from studies in almost exclusively Caucasian individuals.[9],[11],[77] However, recent studies in black male athletes have indicated that they exhibit a higher prevalence of left ventricular hypertrophy (LVH) and repolarisation changes compared

with Caucasian male athletes.[18,19,53,54] The significance of such ECG and echocardiographic appearances in male athletes is unclear, as in a significant proportion, the appearances observed may be similar to that seen in cardiomyopathy, in particular hypertrophic cardiomyopathy (HCM)[42]. There previously has been no data available with respect to female athletes.

This chapter will firstly focus on the data that describes cardiac adaptation to exercise in female black and white athletes, examining both the structural and electrical changes that occur. Following this, I will discuss the data that relates to the significance of the ECG and echocardiographic changes that have been observed in male black athletes. Then, by applying the results from the data presented in chapters 3 to 6, I will suggest a clinical algorithm that aims to facilitate the differentiation between physiological cardiac adaptation and cardiomyopathy in both male and female athletes. Finally, I will examine biochemical and physiological data that may provide a mechanistic explanation for the cardiac changes observed in response to exercise in black individuals.

7.2 Cardiac Structural Adaptation in Black Female Athletes

This study is the first to specifically examine the adaptive changes in response to exercise female international African/Afro-Caribbean athletes. Data from both ECG and trans-thoracic echocardiography have been used to delineate the characteristics of cardiac adaptation in black female athletes.

In comparison with the largest published study in Caucasian female athletes (n =600),[31] only 240 black females were studied. However, when one considers that black female athletes currently comprise less than 10% of all athletes participating at National level in the UK and France, the study cohort represents a sizeable proportion of athletes available for comparisons and inferences.

7.2.1 Left Ventricular Wall Thickness in Black Female athletes.

Similarly to previous reports examining caucasian athletes[31,32], both black and white female athletes demonstrated a relative increase in maximal left ventricular wall thickness (LVWT), left ventricular cavity size and left ventricular mass compared to similar cohorts of sedentary controls. In particular, black female athletes exhibited an 11% increase in maximal LVWT and a 31% increase in calculated left ventricular mass, compared to similar sized black female control subjects. Female white athletes exhibited a similar pattern, with a 6% increase in maximal LVWT and 18% increase in left ventricular mass, compared to white sedentary female control subjects. There were no statistically significant differences between the respective control groups in measures of left ventricular size.

As observed in black male athletes[19], highly trained female black athletes demonstrated an overall greater maximal LVWT and left ventricular mass compared to white female athletes of similar age, size and sporting

discipline. Overall, there was a 7% difference in maximal LVWT and a 9% difference in left ventricular mass between the two ethnic groups.

7.2.2 Black Female Athletes with Left Ventricular Hypertrophy

Consistent with previous reports, none of the Caucasian female athletes, or female control subjects (black or white) exhibited a LVWT >11 mm.[5], [4],[32],[6] In contrast, 8 (3%) black female athletes demonstrated a maximal LVWT >11mm (12-13 mm) that could have been consistent with morphologically mild HCM. None of the 8 black female athletes revealed any further phenotypic features of HCM on further clinical evaluation (Table 4.5). [42]

Importantly, since none of the black female athletes exhibited a LVWT >13mm, it would be reasonable to infer that an absolute maximal LVWT of 13mm probably represents the physiological upper limit of LVH in an asymptomatic black female athlete outside the context of a family history of HCM. A LVWT >13mm may therefore be considered to represent pathologic LVH.

Black female athletes with LVH participated in basketball, football, judo, netball, sprinting, and wrestling, sports that are not traditionally associated with physiologic LVH in Caucasian athletes, indicating that the isotonic and isometric stresses of sport induce more cardiac hypertrophy in black athletes compared with white athletes. Direct comparisons could not be made in sporting disciplines characteristically associated with a greater

LVWT in Caucasians such as rowing, canoeing and cycling [4-6] since most black female athletes in the UK and France do not usually excel in such sporting disciplines. Nevertheless, none of the studies in female Caucasians participating in these sporting disciplines have reported a LVWT >11mm. [4-6]

7.2.3 Other Cardiac Dimensions in Black Female Athletes.

In addition to differences in left ventricular wall thickness and mass, black female athletes demonstrated a significant increase in left atrial diameter compared to similar white female athletes. This difference amount to a 9% increase in left atrial size between the respective groups of athletes. The distribution of left atrial diameter seen here are similar to that previous reported in larger groups of Caucasian female elite athletes,[22] with no black female athlete demonstrating left atrial dilation that may be considered pathological (i.e. >45mm) (Figure 4.2). In particular, no female athlete with LVH had evidence of left atrial dilatation,[78] and all indices of systolic and diastolic function were normal in all subjects studied.[70] Indeed, amongst athletes, diastolic function was enhanced. Absolute measures of E and A velocities were slightly lower amongst athletes vs. sedentary controls across the racial groups, but this can be accounted for by the relative bradycardia amongst the athletic cohort, reflecting improved diastolic filling rather than an abnormality. There were no significant differences between the athletic cohorts with respect to aortic root dimensions.

7.3 The Electrocardiographic Appearance in Black Female Athletes

Racial differences in the resting 12-lead electrocardiogram amongst black male sedentary individuals are well recognised[100-102].The pattern of previously reported data in males is replicated amongst this group of female control subjects, with a longer P-R interval, shorter QTc, and shorter QRS duration seen in black sedentary female individuals.[103] There was also a small difference in the prevalence of voltage criteria for LVH between black and white controls – but these did not reach statistical significance. These findings would suggest that the control groups are typical of the wider UK female sedentary population, and comparisons made between this group and athletes are valid.

In general, female athletes had lower heart rates and longer PR intervals than female control subjects, both black and white. These findings are common amongst high level athletes,[1] and reflect the quality and intensity of training amongst this particular group. Traditionally these alterations have been attributed to an increase in vagal tone at rest,[1] but in addition there may be intrinsic changes in the properties of the SA and AV node that contribute to the appearance of the surface 12-lead ECG.[43,104]

With respect to repolarisation anomalies, Black female sedentary control subjects demonstrated a small, but non-significant, increase in the prevalence of T-wave inversions compared to white female control subjects. In addition, there were numerical differences in the prevalence

of repolarisation anomalies, both J point ST elevation and T wave inversions, between black female athletes and black sedentary control subjects – but these differences failed to reach statistical significance (p=0.28; and p=0.14 respectively).

In contrast, white female controls exhibited a higher prevalence of J-point and ST segment elevation compared to white female athletes, contrasting previously reported data.[9] There were no differences in the prevalence of T-wave inversions between white athletes and controls. The prevalence of J point and ST elevation amongst this particular cohort of white athletes is lower than has previously been reported amongst other groups of white female athletes, accounting for this difference.

7.3.1 Differences in Electrocardiographic Repolarisation between Black and White Female Athletes

Black female athletes exhibited a greater prevalence of T wave inversions compared with white athletes. T wave inversions were present in 14% of black athletes compared to 4.5% of white athletes, and confined to the anterior precordial leads (V1-V3). Their presence did not appear to be determined by age, body size, sporting discipline or cardiac dimensions. Deep T wave inversions were only observed in a small number of black female athletes (figure 5.2). In particular, athletes with T wave inversions did not reveal any phenotypic features of HCM[42] or ARVC[105] on subsequent evaluation.

In general, there appears to be a racial predilection for the development of T wave inversions amongst black individuals, as has been suggested by previous larger studies on sedentary male individuals.[100] The data in the cohort of female sedentary control subjects shows a similar trend, although this failed to reach statistical significance. Participation in regular physical activity would appear to enhance this effect, with a dramatic increase in the prevalence of T wave inversions seen amongst elite female black athletes when compared to both white athletes and sedentary black controls. In addition, deep T wave inversions were seen only amongst black athletes and not in any white individual or sedentary control subject (black or white), suggesting that these are a consequence of physical training, rather than simply due to ethnic variation.

T wave inversions amongst black athletes were confined to the anterior precordial leads (V1-V3), which differed in distribution pattern from that seen in white athletes or black sedentary controls. In both groups, T wave inversions were observed in the inferior and anterior leads in similar proportions. This would suggest that physical activity induces the development of T wave inversions predominately across the anterior pre-cordial leads, rather than the inferior leads. Lateral T wave inversions were not seen in any subject – athlete or control, suggesting that their presence is unusual and more likely to be associated with underlying cardiac pathology.

The prevalence and magnitude of these electrical changes in black female athletes remains significantly lower than that observed amongst

black male athletes,[19] but higher than those reported in Caucasian male athletes.[9,11]

The prevalence of ST segment elevation amongst black athletes was significantly higher than in white female athletes. This again reflects the low incidence of J point ST segment elevation seen amongst white female athletes.

In summary, physical training in black individuals is associated with the presence of T wave inversions confined to the anterior precordial leads, which in a minority of athletes may be greater than -0.2mV in depth and termed “deep”. This would appear to reflect physiological adaptation, rather than cardiac pathology.

7.4 Cardiac Adaptation to Exercise in Black Male Athletes

Previous data has described attempted to describe the spectrum of ECG and echocardiographic changes that occur in response to regular physical activity in black male athletes[18,19,53,54]. With respect to the electrocardiogram, cross sectional studies of black American male collegiate football players have indicated that there is a higher prevalence of repolarisation changes observed, when compared to similar white male athletes. [18,54] In certain cases, these changes may overlap with the phenotype observed in HCM. As yet, there has been little data examining the distribution and significance of these anomalies amongst a large and

diverse body of athletes, participating in a range of different sporting activities.

The aim of this data was an attempt to elucidate the significance of electrical repolarisation changes amongst a large group of black male athletes. The study population comprised a large group of black elite male athletes, numbering 904 individuals, who competed in 25 different sporting disciplines. The prevalence and distribution of electrical repolarisation anomalies amongst this cohort was compared with that observed amongst a group of sedentary black individuals and black individuals with HCM. The purpose was to provide data to facilitate the differentiation between expressions of simply ethnicity alone, ethnic variation in physiological cardiac response to exercise, and quiescent cardiac pathology.

In contrast to studies published in the current literature,[18,54] this was the first study where all study participants underwent both ECG and 2D echocardiography. Where repolarisation anomalies were identified, the athletes concerned were offered a voluntary, more comprehensive cardiac evaluation. This was completed in the majority (66%) of individuals. In addition, this is the first data on the longitudinal assessment of black athletes, both with and without repolarisation anomalies, to provide a real clinical perspective on the significance of these common electrocardiographic appearances.

7.4.1 Ethnic Differences in Repolarisation Changes in Elite Male Athletes

Overall, black male athletes demonstrated a significantly higher prevalence of repolarisation changes, when compared to both white males athletes and sedentary controls (Table 6.1). In total, almost one quarter exhibited significant T wave inversions, and nearly two thirds showed ST-segment elevation. With respect to T wave inversions, these were observed only in just under 4% of white athletes, and 10% of black control subjects.

7.4.2 The distribution of repolarisation changes amongst black athletes

Repolarisation changes in black athletes differed not only in their observed frequency, but also their distribution across the standard 12-lead ECG.

7.4.2.1 The Anterior Precordial leads

Overall, black male athletes exhibited a significantly greater prevalence of T-wave inversions confined to only the anterior leads when compared to black male sedentary control subjects. This indicates that the presence of anterior T-wave inversions (including deep T wave inversions) is likely to represent an ethnic response to physiological adaptation to exercise, rather than an effect of purely ethnicity alone. T-wave inversions confined

solely to the anterior leads were rare amongst black individuals with HCM, again indicating that this is likely to represent a physiological rather than a pathological process. Further evidence that this does indeed represent a physiological process is the observation that these anterior T wave changes may regress, as early as 6 weeks after cessation of exercise (Figure 7.1).

The presence of anterior T-wave inversions is also a minor criteria in the diagnosis of arrythmogenic right ventricular cardiomyopathy (ARVC)[105,106]. Importantly, none of out athletes demonstrated any further diagnostic criteria despite extensive and comprehensive investigations. The precise prevalence of ARVC amongst different ethnic groups is unknown, however the high prevalence of T –wave inversions in the anterior leads amongst black athletes, the co-existence of preceding ST-elevation in a large proportion, and the demonstration of regression with detraining suggests that these repolarisation changes are unlikely to represent ARVC.

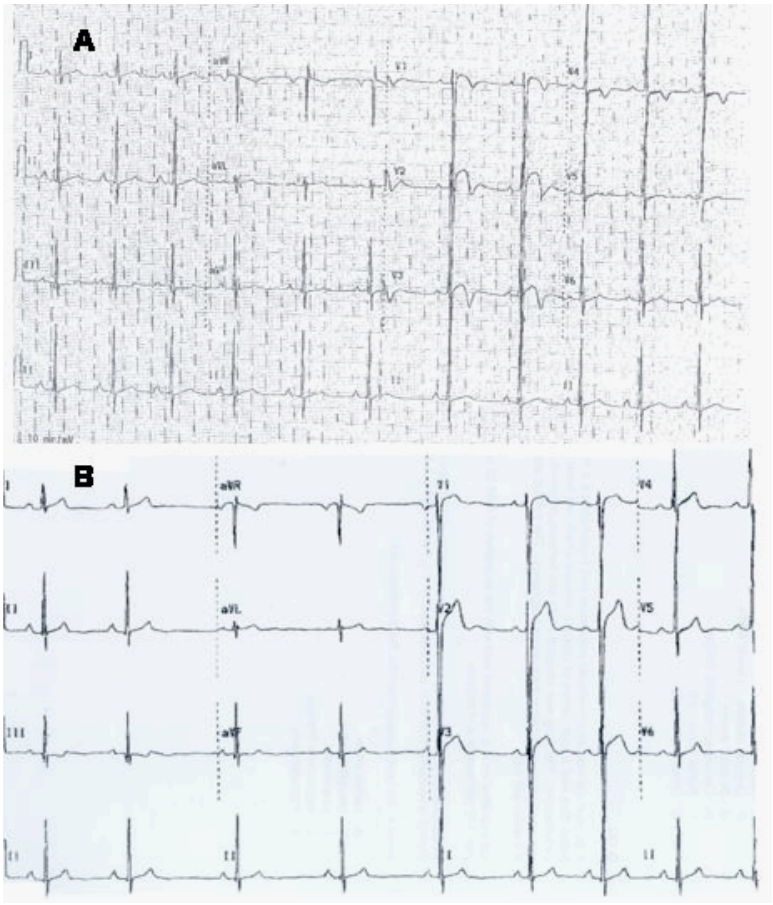


Figure 7.1 – 12-lead ECGs taken from a 17 year old black male professional footballer during peak training (A) and after an 8 week period of detraining (B). Panel A demonstrates convex ST segment elevation associated with deep T wave inversions in the anterior precordial leads which regress after a period of detraining. Echocardiography and cardiac MRI demonstrated a structurally normal heart.[107]

7.4.2.2 Inferior leads

Overall, T wave inversions in the inferior leads were far less frequent across all groups. However, they were again more frequently seen in black athletes when compared to white athletes. There was no significant difference in the prevalence when compared to black control subjects.

Isolated inferior T-wave inversions frequently involving leads III and aVF have been reported in a number of studies examining the appearances of the athletes ECG. As yet, no data has suggested that their presence is associated with a malignant cardiac phenotype. In line with this, within our cohort, despite intensive investigation, we failed to demonstrate any significant cardiac pathology in any individual with isolated inferior T-wave changes.

7.4.2.3. Lateral leads

Overall, the prevalence of lateral (V5, V6, I and aVL) T-wave inversions was low across the entire study cohort. However, there were no differences in the frequency that these changes were observed amongst black male individuals when one compared athletes with sedentary control subjects. This is in contrast to white male athletes, where lateral T wave inversions were extremely rare and observed in only 0.3% of subjects compared to a frequency of 3-4% amongst black individuals. This implies that the presence of lateral T-wave inversions may reflect ethnic variation amongst the majority of black athletes.

However, the majority of black patients with HCM, and all 3 athletes identified with this condition (of both races) during follow up, exhibited T-wave inversions in the lateral leads. Therefore, the finding of lateral T-wave inversions in an athlete, of any ethnicity, should be viewed with caution, since a proportion of these individuals may harbour HCM.

This conclusion, that the presence of lateral T wave inversions may indicate a cardiomyopathy, is also supported by data from Italy. In a study of 81 athletes who demonstrated marked repolarisation abnormalities who were followed up for a an average of 9 years, 5 subsequently developed phenotypic evidence of a cardiomyopathy. All of these individuals exhibited lateral T-wave inversions.[108]

7.4.3 ST Segment Shift

ST-segment elevation was a common finding amongst all black individuals assess, irrespective of athletic training. Similar findings have been previously described amongst black populations and suggest an ethnicity related effect.[50,100,101]

A detailed examination of the ST segment demonstrated a variety of different morphologies of ST segment elevation were present amongst this cohort (Figure 6.3). Concave /saddle shaped ST segments that mimics that seen in acute pericarditis, was a common finding in both black athletes and sedentary controls. The pattern of convex ST-elevation (Figure 6.3A), akin to that observed in acute ischaemia or the Brugada phenotype, was six times more common amongst athletes, indicating that this may be the result of a physical response to training in black athletes. The notion is supported by its regression upon cessation of physical activity. (Figure 7.1)

7.5. Trans-thoracic Echocardiography in Black Male Athletes

All participants in this study underwent 2-D trans-thoracic echocardiography as part of the standardised cardiac screening protocol. This is the largest cohort of elite black male athletes that has been examined to date in the current literature.[18,19] The individuals assessed all competed in sport at a national or international level, and participated in a wide range of sporting disciplines. In general, these reflect sporting participation amongst this particular ethnic group across the UK and France.

In a similar pattern to that observed amongst black female athletes, black male athletes did not participate in the sports that traditionally generated the greatest changes in LV wall thickness and cavity size - in particular cycling and rowing. This is a reflection of general participation levels world wide at both national and international levels.

7.5.1. Measures of Left Ventricular Wall Thickness

In keeping with other previous studies examining cardiac dimensions in black male athletes,[19] the mean maximal left ventricular wall thickness (LVWT) was significantly greater than in similar white male athletes. The distribution of maximal LVWT is shown in figure 6.5. Calculated left ventricular mass was also higher in black male athletes, with a 16g average increase when compared to similar white athletes corrected for

body surface area. There were no significant observed differences in mean maximal LVED between the black and white athletes.

Both groups of athletes demonstrated significantly greater average maximal LVWT, maximal LVED, and calculated left ventricular mass when compared to sedentary black control subjects. This suggests that the data amongst the athletic cohort truly reflects the physiological process of cardiac adaptation to regular physical activity.

The maximal observed LVWT amongst black male athletes was 16mm. The two black athletes that were subsequently diagnosed with HCM had a maximal LVWT of 14mm and 15mm respectively. However, this was associated with other echocardiographic features in the individuals concerned that suggests pathological hypertrophy i.e. a non dilated LV cavity size, enlargement of the left atrium and lateral T-wave inversions in 12-lead ECG (Figure 6.5).

In the absence of any further phenotypic features, it would be reasonable to infer from this data, that 16mm represents the maximum limit of physiological hypertrophy amongst black male athletes.

Amongst white male athletes, none exhibited a maximal LVWT of greater than 13mm, in keeping with previously published large cohort data.[4,34] Importantly, the single white athlete that was subsequently diagnosed with HCM had a maximum LVWT of 11mm well within the quoted upper limits of normal for his gender and ethnicity. He did however had significant

ECG abnormalities (Figure 6.5) - including lateral T wave inversions, which would not in general be considered in keeping with a diagnosis of athlete's heart. In this individual, the diagnosis was confirmed after identification of HCM in his mother and subsequent genetic testing. This highlights the importance of a through and comprehensive assessment of athletes with repolarisation anomalies, including a family history, and not relying purely upon absolute measures of cardiac dimensions.

Amongst the patient cohort with HCM, the average maximal left ventricular wall thickness was 17.4mm. This falls outside the range observed in healthy black or white male athletes or controls. Only one black patient with HCM had normal left ventricular wall thickness (1.9%). Importantly, this data does highlight that that the vast majority of individuals with HCM will exhibit LVH in some form. This was reflected in calculated left ventricular mass, with the mean LV mass amongst black patients with HCM being over 70g higher than in any athlete cohort.

7.5.2 Other measures of cardiac chamber size and function

Average left atrial diameter was increased in black athletes relative to both male white athlete and male black controls. Similarly, there was a small but statistically significant difference in aortic root diameter between black and white groups of male athletes. These findings are similar to that previously reported amongst smaller cohorts,[19] and would seem to represent a true ethnic difference in response to exercise. None of the

athletes, including those with LVH, demonstrated isolated LA dilatation that would be considered pathological (i.e. greater than 45mm).

With respect to other measures of diastolic function (mitral inflow velocity, tissue Doppler of the mitral annulus), black male athletes had a slightly lower peak E-wave velocity which was reflected in a lower average E/A ratio, when compared to both white male athletes and black male control subjects. This again is likely to reflect the significant bradycardia noted in black athletes relative to other cohorts. There were however no differences observed in either tissue Doppler velocities nor ratios between the respective cohorts. No individual demonstrated any significant abnormality of either systolic or diastolic function. Specifically, this includes all athletes with LVH.

7.6 Implications for Pre-Participation Screening

Overall, these findings have implications for the cardiac pre-participation screening of all black individuals, both males and females.

Although the relative risk of sudden cardiac death during sport in females is considerably lower than in males, female athletes are not exempt from cardiac fatalities during sport,[12,59,109] therefore, the observation that normal healthy black female athletes may demonstrate physiological LVH >11mm and T wave inversions that mimic morphologically mild HCM is a major finding and has potential implications in relation to pre-participation cardiovascular screening programs.[110]

With respect to male black athletes, this is the first data presented examining the long term significance of repolarisation anomalies and echocardiographic LVH. The implications of the findings to pre-participation screening criteria will be discussed in the following sections.

7.6.1 Differentiation of Physiological Left Ventricular Hypertrophy from Hypertrophic Cardiomyopathy

Amongst the population of black female athletes in this study, 3% exhibited a maximal LVWT of 12mm or 13mm, which falls inside the range of values seen in morphologically mild HCM. Amongst the black male population, 12.4% of individuals demonstrated LVH, of up to 16mm. The accurate differentiation between physiological and pathological LVH is essential due to potentially serious consequences that a diagnosis of HCM has for the athlete concerned and their family. If the current guidelines,[17,77] derived from predominately Caucasian athletes, had been applied to this population, this could have resulted in the unnecessary exclusion of these athletes from competitive sport.

None of the female athletes with LVH demonstrated any further indication of HCM on trans-thoracic echocardiography – namely evidence of increased left ventricular filling pressures (an increased left atrial diameter (>45mm) or impaired diastolic function (an E/E' ratio of >7), a small left ventricular cavity size (<45mm), or left ventricular outflow tract obstruction.

Amongst the black male athletic population, 2 individuals were diagnosed with HCM – one prospectively with clear echocardiographic evidence of HCM, the other retrospectively following a cardiac arrest. However, amongst the remaining male black athletes with LVH, there was no further evidence of HCM, other than isolated measures of left ventricular wall thickness.

In addition to echocardiography, all individuals with LVH underwent extensive investigations to exclude any further phenotypic evidence of HCM, including cardiac MRI, 24 hour Holter monitor ECG recordings, and standard upright treadmill exercise testing. In particular, there was no evidence of myocardial fibrosis on late gadolinium enhancement cardiac MRI imaging, a sensitive and specific marker of HCM.[75,111]The measures of LVWT obtained on trans-thoracic echocardiography correlated well with that derived from cardiac MRI.

7.6.2 A Bedside Clinical Algorithm for the Differentiation of Left Ventricular Hypertrophy in Black Athletes

The application of data derived from this study to the pre-participation screening of black athletes will facilitate the differentiation between pathological and physiological LVH in such individuals.

Trans-thoracic echocardiography is the most widely used and available means of cardiac imaging and in the majority of cases will provide the

clinician with sufficient information to make the diagnosis at the bedside, without having to rely on additional more expensive and complex imaging modalities. As has been previously demonstrated in both white athletes and black male athletes, the characteristics of physiological LVH are similar in black athletes – namely relative dilatation in the left ventricular cavity size, a normal left atrial diameter, and normal indices of left ventricular systolic and diastolic function. The data presented here indicates that the upper limit of such physiological LVH should be 13mm in black females. In black males, as has been suggested in smaller cohort studies,[19] the upper limit should be considered 16mm.

The definitive diagnosis of HCM, the commonest cause of exercise related sudden cardiac death amongst athletes,[28,59] is based on genomic analysis and identification of a causal mutation.[60] Although there have been considerable advances in the methodology for genetic diagnosis, routine gene testing in the absence of familial disease is generally not recommended in the UK. The wide genetic hetrogeneity and high prevalence of private mutations does mean that a negative genetic diagnosis is not sufficient to exclude this potentially lethal condition.[60] Furthermore, gene testing for HCM is still prohibitive in terms of time and may prove costly for the athletes fitness and potential future career. The ESC currently recommends that genetic testing should be reserved for those cases that remain equivocal, despite extensive clinical investigation, and conducted in an expert setting by clinicians experienced in interpreting correctly the results.[112] Amongst the 3 male athletes diagnosed with HCM amongst this cohort, HCM was diagnosed in a single

white athlete using genomic analysis having had a causal mutation identified in a first degree relative (his mother) with clear phenotypic evidence of HCM.

At present, a thorough clinical assessment including both 12-lead ECG and trans-thoracic echocardiography should underpin the evaluation of athletes with left ventricular hypertrophy. Genetic testing does not form a part of the routine clinical assessment of athletes, but may have an important role in the future, given the advances in technology relating to mutational analysis.

7.6.3 Interpretation of the 12-lead ECG in Black Athletes

This study is the first to illustrate that black female athletes may demonstrate T-wave inversions in a resting 12-lead ECG, the appearance of which may overlap with that observed in cardiomyopathy, namely HCM and ARVC.

However, unlike HCM, none of the black female athletes in this study exhibited deep T wave inversions in the inferior or lateral leads; therefore, the identification of deep T wave inversions in these leads in a black female with LVH would probably be representative of pathology rather than physiology. None of the female athletes with T wave inversions had any other features on their 12-lead ECG that may be associated with HCM, i.e. ST segment depression, extreme left axis deviation, or LBBB[42] With respect to ARVC, on further extensive investigation, none had any of

the diagnostic criteria identified by the European task force in the diagnosis of this condition,[106] other than T wave inversions across the anterior precordial leads.

Amongst the cohort of black male athletes, T wave inversions were present in 22.8% of individuals, and confined to the anterior leads in 12.8% of individuals. No male athlete with T wave inversions or convex ST segment elevation confined to the anterior pre-cordial leads demonstrated any evidence of cardiomyopathy at initial assessment or longitudinal follow-up.

T-wave inversions in the lateral or inferior leads were observed significantly less frequently. All athletes with subsequently diagnosed with HCM demonstrated T-wave inversions, in all cases with a voltage of >0.2mV (i.e. deep), in the lateral leads. Their presence should therefore considered to represent pathology, and the athlete should under-go an extensive evaluation to exclude the presence of a cardiomyopathy.

Black athletes in general have a higher prevalence of T wave inversions and ST-segment elevation when compared to white athletes, both male and female.[100] These differences appear to be exaggerated by physical training, and when present, usually confined to the anterior pre-cordial leads V1-V4 (to V3 in females). Based on this study, T wave inversions in leads V1-V3 may be considered a normal physiological finding when encountered at a routine pre-participation cardiac screen in an otherwise healthy and asymptomatic black athlete.

Data on the longitudinal follow up of male white athletes with repolarisation anomalies identified cardiac pathology in 11/81 (13.5%) athletes studied, None of the athletes that subsequently developed cardiac pathology exhibited similar ECG pattern to that observed amongst the cohort of female athletes.[108] All had extensive T wave inversions that extended across the anterior, lateral and (in 54%) the inferior leads. Amongst the population of male athletes studied in this cohort, a total of 3 athletes of the 273 with significant T-wave inversions were eventually diagnosed with a cardiomyopathy, all of whom also demonstrated T-wave inversions that extended across the lateral and inferior leads (Figure 6.5). These data suggest that athletes with T wave inversions that involve that lateral leads, in particular that extend beyond a single territory, should be investigated thoroughly and repeatedly at intervals to exclude the presence of an occult cardiomyopathy. Of note, in both our data and the previously published work[108], 2 individuals were only diagnosed after a cardiac arrest, one of which was fatal for the individual concerned.

None of the female athletes in this particular cohort (black or white) had such extensive repolarisation anomalies, which in general, fall outside the spectrum of repolarisation anomalies seen in physiological adaptation to exercise.

7.6.4 The Impact on Pre-Participation screening of Black Athletes & Recommendations

The use of the resting 12-lead ECG in pre-participation cardiac screening is advocated by both international cardiac societies[16,17] and major international sporting organisations.[14,15] The criteria used to define the normal range of appearances in the athletes ECG has been derived solely from data examining cardiac adaptation amongst predominately Caucasian individuals.

The findings of this study illustrate that black female athletes may exhibit repolarisation anomalies – namely T wave inversions in the anterior precordial leads – on the resting 12-lead ECG, in a similar pattern to that seen in black male athletes.[19,54] [18] This study has provided valuable data on the significance of such ECG appearances in a large cohort of black male athletes. This suggests that the presence of T wave inversions in the anterior precordial leads represents physiological adaptation to regular exercise, rather than occult cardiac pathology.. The application therefore of criteria derived in Caucasian populations may lead to the generation of false positive results, leading to unnecessary investigations with subsequent athlete anxiety, physiological distress and potential disruption to training schedules.

If the current guidelines are rigorously applied to this cohort of athletes, [16,17] then up to 25% of the black athletes assessed in this study would require further investigations based on the presence of T-wave inversions.

Application of the criteria that are outlined below – namely attributing the presence of isolated anterior T wave inversions in the absence of any significant cardiac history – could reduce the numbers of athletes requiring investigations to as low as 4%. This represents a significant cost saving, particularly in countries with a large proportion of black athletes and limited financial resources.

When screening an individual for cause of sudden cardiac death during sport, an appreciation must be taken of an athlete's ethnicity. In a black asymptomatic individual with no family history of cardiomyopathy or sudden cardiac death, the identification of T wave inversions in the anterior precordial leads (V1-V3) may be considered normal ethnic variation. Contiguous T wave inversions in the lateral or inferior leads remain unusual findings amongst black athletes and should therefore be investigated further, with a minimum of trans-thoracic echocardiography, prior to the athlete being cleared for competition.

At trans-thoracic echocardiography, this study suggests that the upper limit of left ventricular wall thickness in black female athletes should be 13mm, and in black male athletes 16mm. This measure should not however be considered in isolation, but take in context with other echocardiographic indices of left ventricular function – including left ventricular diameter, left atrial diameter and markers of systolic and diastolic function (including TDI). If any of these suggest any diagnosis other than physiological hypertrophy, the individual concerned should be asked to suspend physical activity until the results of further investigation

are known. If however an athlete is asymptomatic, has no family history of sudden cardiac death or cardiomyopathy, and has no features consistent with cardiomyopathy on his/her trans-thoracic echocardiogram, then irrespective of whether further investigations are planned, they should be allowed to continue sporting activity until the results are known.

In keeping with the current guidelines, an athlete any of the following additional features should undergo further investigation to exclude a cardiomyopathy or other potential cardiac cause of sudden death during exercise. These additional features include:

- Symptoms suggestive of occult cardiac disease e.g. unheralded syncope
- A family history of cardiomyopathy or sudden cardiac death
- Any findings on physical examination – e.g. a significant pre-cordial murmur
- A 12-lead ECG with additional features suggestive of cardiomyopathy i.e:
    - T wave inversions in the lateral &/or inferior leads
    - ST segment depression
    - Left axis deviation
    - Left Bundle branch block
    - Pathological Q waves
- Findings on trans-thoracic echocardiography consistent with structural heart disease or cardiomyopathy.

7.7 Potential Mechanisms for Ethnic Differences in Cardiac Adaptation

The precise mechanisms for the exaggerated myocardial hypertrophy and ECG appearances in black athletes in response to exercise are complex, and remain to be elucidated.

7.7.1 Structural differences

Regular exercise is associated with an increase in systemic blood pressure at peak exercise, as a result of both the increase in cardiac output and changes in systemic vascular resistance. There may be racial and gender differences in response to these modulations in BP, which may account for the relative left ventricular hypertrophy seen amongst black individuals, particularly men. [19] However both my own experience of exercising both male and female black and white athletes with physiological LVH, and the longstanding experience of our research group,[19] has not demonstrated any significant differences in peripheral exercise related BP responses between the ethnic groups. All the male and female athletes studied in this cohort had an entirely appropriate blood pressure response to exercise, with none having a peak systolic blood pressure of >180mmHg. Indeed, if the hypertrophic response to blood pressure is the primary mechanism, then one may expect a degree of diastolic dysfunction, as may be seen in hypertensive heart disease.[113] This was absent, and indeed diastolic function was enhanced in athletic

subjects, as has previously described.[23] No athlete or control reported a significant family history of hypertension. Given the relative prevalence of these conditions in the general population, and the age distribution of the study cohort, this would seem unlikely to be correct. A familial response to sub-clinical longstanding hypertension may play a role in the development of LVH in black athletes, but no relationship between LVH and blood pressure was demonstrated in this group.

Systemic vascular resistance and vascular tone play a key role in the determination of an individual's response to hypertension. Racial and gender differences in large[114] and small[115] artery structure and function, endothelial function,[116] the renin-angiotensin system,[117] and levels of vasoactive cytokines,[118] are recognised and may partially explain the differences in the magnitude of LVH between black athletes and white athletes and the greater predilection to LVH in male athletes in both ethnic groups respectively.

Mechanisms of physiological hypertrophy are complex, and recent in-vivo studies suggest that these are different to that seen in pathological states – such as the left ventricular hypertrophic response to systemic hypertension. Importantly in murine models of both physiological and pathological hypertrophy, there is characteristically the absence of myocardial fibrosis amongst mice with a physiological hypertrophic response to exercise. [119]

In-vitro and animal studies indicate that physiological LVH is mediated by the effects of Insulin like growth factor 1 (IGF-1)[120] on the phosphatidylinsitol-3-kinase (PI3K)-Akt1[119] pathway which appears to regulate downstream transcription factor and gene product production.[121] It is possible that potential race related polymorphisms in IGF-1 function within the African population may also provide an explanation for the greater magnitude of LVH observed in black athletes.

7.7.2 Electrical Differences

It is historically recognised that a significant proportion of normal black males and females exhibit T wave inversions in the right precordial leads extending to V3 and V4.[52,122] Our own experience also suggests that male black athletes may acquire such T wave inversions in the right precordial leads during physical training (figure 7.1) that are not related to cardiac structure and which regress after a six to eight week period of de-conditioning. Alterations in autonomic cardiac innervation, either reduced sympathetic or increased vagal tone, or, recently identified sodium channel polymorphisms amongst the black population[123,124] may provide some explanation for the variation found within black athletes, however more detailed molecular assessment and longitudinal follow up of black athletes is necessary to unravel the intriguing manifestations of the black athlete's heart.

With respect to the differences between male and female athletes, of both ethnicities - one potential explanation may lie within variations in

reproductive hormones, oestrogen and progestrogen and the female menstrual cycle. Vagal tone and baroreceptor sensitivity have both been shown to alter during the natural menstral cycle[125], and are sensitive to the administration of exogenous oestrogen (eg. as the oral contraceptive pill)[126]. These may contribute to the changes observed. However, female elite athletes often exhibit wide variation in their menstrual cycle, given the demands of their sporting endeavours, that may limit the impact of these hormones of the appearances of the resting ECG.

7.8. Conclusion

Systematic physical exercise in black athletes is associated with greater LVH and higher prevalence of repolarisation changes compared with white athletes of similar age and size participating in identical sporting disciplines. However, a maximal LVWT >13 mm in female athletes, and >16mm in male athletes, or deep T wave inversions in the inferior and lateral leads are rare and warrant further investigation.

Chapter 8 – Limitations of this Study and Suggestions for Further Research

This study has strived to provide information on cardiac remodelling in black athletes, both male and female athletes in order to facilitate the accurate pre-participation screening of such individuals. Due to certain financial, logistical and ethical issues, there are certain limitations that should be highlighted.

The absolute measures of LV wall thickness were not blinded, although intra- and inter- observer variability was within accepted limits. Neither was the sonographer blinded to the ethnicity of the individual being studied. This in an inherent problem with all large scale observational studies of this type. In order to avoid un-intentional measurement bias, future studies could make further use of blinding, in particular with the use of off-line measurements in order to minimise this potential source of error.

With respect to the data on female athletes, this study is cross sectional in design, and as such provides only a limited short term view of cardiac remodelling amongst this population. No female athlete was diagnosed with a cardiomyopathy or other cardiac disorder over the time period that this study was conducted. Specific longitudinal follow-up amongst female athletes is needed to ensure that the observed repolarisation

changes and left ventricular hypertrophy do not represent cardiac pathology.

With respect to the data on male black athletes, follow-up data was presented here for the first time. The duration of follow-up was relatively short however, as event rates in HCM are low. Follow-up data was also incomplete, including evaluation of first degree relative, in a significant number of athletes. However, follow-up data was available in a substantial number of the athletes assessed (n=1243), which suggests that valid conclusions can be drawn from the study findings. The number of athletes that were assessed on multiple occasions is significant, given the practical difficulties in motivating healthy individuals to attend for prolonged clinical assessment, given the time involved and the absence of perceived benefit relating to athletic performance.

The diagnosis of HCM was established only in athletes with repolarisation changes and/or LVH who exhibited a potentially fatal arrhythmia, familial disease or asymmetric septal hypertrophy with a non dilated left ventricle and evidence of left atrial enlargement. Hypertrophic cardiomyopathy, however, is a heterogeneous condition, with wide variation in its phenotypic expression. Therefore, milder or more benign forms of the disorder may not have been identified. Plausibly, athletes without repolarisation abnormalities on their 12 lead ECG, or T wave inversions in the anterior/inferior leads may harbour a quiescent cardiomyopathy. The follow-up data collated did not provide any indication that this statement may be correct.

Similarly, this study is purely observational and makes no attempt to provide any physiological explanation for the anomalies observed. As discussed, there is a considerable amount of data in the literature attempting to provide an explanation for ethnic differences that have been observed in response to hypertension. There has been no studies do date that relate specifically to athletes. These is therefore a need for specific mechanistic studies in the future, in both animal and human models.

There is also the recognition that misuse of performance enhancing substances may be associated with LVH and marked repolarisation changes,[127] however, all athletes studied were part of national and international squads and as such underwent regular testing for the presence of such substances. Hence, all subjects where considered free from compounds that may adversely affect these results.

Only 52 patients with a diagnosis of HCM were included in the analysis, which limits the conclusions that can be drawn relating to the quantitative characteristics of black individuals with HCM. However, if one considers that only 2-3% of the UK population is afro-Caribbean/ African origin, then represents a relatively large cohort of individuals. It is important to recognise that the definition of HCM (i.e. the identification of LVH in the absence of any other cardiac or systemic cause) per se prevents a definitive diagnosis in a many affected black individuals. In particular, hypertension is present in up to 50% of the black population

aged over 40, and as a recognised cause of LVH, HCM cannot be considered in these individuals. A multi-centre American study involving 1986 HCM patients supports the difficulties encountered in establishing a diagnosis of HCM in black individuals. In this cohort, only 8% of those studied were black.[63] The HCM cohort was also significantly older than the athletic population. However, given that the identification of HCM, in relatively asymptomatic individuals, depends upon the level of contact with a healthcare system. This increases with age, hence the age difference in the identification of this condition. The purpose of this cohort however was not to provide a like for like comparison, but to allow the identification of key clinical features that may can be used in the differentiation between pathological and physiological hypertrophy.

Finally, as per current published guidelines, genetic testing was not available to aid the differentiation of athlete's heart from HCM outside of the context of established familial disease.

References

1. Huston TP, Puffer JC, Rodney WM. The athletic heart syndrome. *N Engl J Med.* 1985;313:24-32.

2. Henschen S. Skidlauf und Skidwettlauf. Eine medizinische sportstudie metteilungen aus der medizinishchen klink zu upsala jena. *Mitt Med Klin Upsala Fischer Verlag Jena.* 1899;2.

3. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. *Ann Intern Med.* 1975;82:521-524.

4. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med.* 1991;324:295-301.

5. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation.* 2000;101:336-344.

6. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2002;40:1431-1436.

7. Spirito P, Pelliccia A, Proschan MA, et al. Morphology of the "athlete's heart" assessed by echocardiography in 947 elite athletes representing 27 sports. *Am J Cardiol.* 1994;74:802-806.

8. Oakley DG, Oakley CM. Significance of abnormal electrocardiograms in highly trained athletes. *Am J Cardiol.* 1982;50:985-989.

9. Sharma S, Whyte G, Elliott P, et al. Electrocardiographic changes in 1000 highly trained junior elite athletes. *Br J Sports Med.* 1999;33:319-324.

10. Zehender M, Meinertz T, Keul J, Just H. ECG variants and cardiac arrhythmias in athletes: clinical relevance and prognostic importance. *Am Heart J.* 1990;119:1378-1391.

11. Pelliccia A, Maron BJ, Culasso F, et al. Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation.* 2000;102:278-284.

12. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *JAMA.* 1996;276:199-204.

13. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA.* 2006;296:1593-1601.

14. Bille K, Figueiras D, Schamasch P, et al. Sudden cardiac death in athletes: the Lausanne Recommendations. *Eur J Cardiovasc Prev Rehabil.* 2006;13:859-875.

15. Dvorak J, Junge A, Grimm K, Kirkendall D. Medical report from the 2006 FIFA World Cup Germany. *Br J Sports Med.* 2007;41:578-81; discussion 581.

16. Corrado D, Pelliccia A, Heidbuchel H, et al. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J.* 2010;31:243-259.

17. Corrado D, Pelliccia A, Bjornstad HH, et al. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J.* 2005;26:516-524.

18. Magalski A, Maron BJ, Main ML, et al. Relation of race to electrocardiographic patterns in elite American football players. *J Am Coll Cardiol.* 2008;51:2250-2255.

19. Basavarajaiah S, Boraita A, Whyte G, et al. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2008;51:2256-2262.

20. Wade OL BJ. *Cardiac output and regional blood flow.* Philadelphia: FA Davis; 1962.

21. Dempsey JA. J.B. Wolffe memorial lecture. Is the lung built for exercise? . *Med Sci Sports Exerc.* 1986;18:143-155.

22. Pelliccia A, Maron BJ, Di Paolo FM, et al. Prevalence and clinical significance of left atrial remodeling in competitive athletes. *J Am Coll Cardiol.* 2005;46:690-696.

23. Vinereanu D, Florescu N, Sculthorpe N, Tweddel AC, Stephens MR, Fraser AG. Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long-axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. *Am J Cardiol.* 2001;88:53-58.

24. Makan J, Sharma S, Firoozi S, Whyte G, Jackson PG, McKenna WJ. Physiological upper limits of ventricular cavity size in highly trained adolescent athletes. *Heart.* 2005;91:495-499.

25. Maron BJ. Structural features of the athlete heart as defined by echocardiography. *J Am Coll Cardiol.* 1986;7:190-203.

26. Myerson SG, Montgomery HE, World MJ, Pennell DJ. Left ventricular mass: reliability of M-mode and 2-dimensional echocardiographic formulas. *Hypertension.* 2002;40:673-678.

27. De Castro S, Pelliccia A, Caselli S, et al. Remodelling of the left ventricle in athlete's heart: a three dimensional echocardiographic and magnetic resonance imaging study. *Heart.* 2006;92:975-976.

28. Basavarajaiah S, Wilson M, Whyte G, Shah A, McKenna W, Sharma S. Prevalence of hypertrophic cardiomyopathy in highly trained athletes: relevance to pre-participation screening. *J Am Coll Cardiol.* 2008;51:1033-1039.

29. Nagashima J, Musha H, Takada H, Murayama M. New upper limit of physiologic cardiac hypertrophy in Japanese participants in the 100-km ultramarathon. *J Am Coll Cardiol.* 2003;42:1617-1623.

30. Rodriguez Reguero JJ, Iglesias Cubero G, Lopez de la Iglesia J, et al. Prevalence and upper limit of cardiac hypertrophy in professional cyclists. *Eur J Appl Physiol Occup Physiol.* 1995;70:375-378.

31. Pelliccia A, Maron BJ, Culasso F, Spataro A, Caselli G. Athlete's heart in women. Echocardiographic characterization of highly trained elite female athletes. *JAMA.* 1996;276:211-215.

32. Whyte GP, George K, Nevill A, Shave R, Sharma S, McKenna WJ. Left ventricular morphology and function in female athletes: a meta-analysis. *Int J Sports Med.* 2004;25:380-383.

33. Pelliccia A, Maron BJ, Di Paolo FM, Culasso F. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med.* 1999;130:23-31.

34. S Sharma, BJ Maron, G Whyte, S Firoozi, P Elliott, WJ Mckenna. Physiological limits of left ventricular hypertrophy in junior elite athletes: relevance to the differential diagnosis of athletes heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2002;40:1431-1436.

35. Lewis JF, Maron BJ, Diggs JA, Spencer JE, Mehrotra PP, Curry CL. Preparticipation echocardiographic screening for cardiovascular disease in a large, predominantly black population of collegiate athletes. *Am J Cardiol.* 1989;64:1029-1033.

36. Henriksen E, Kangro T, Jonason T, et al. An echocardiographic study of right ventricular adaptation to physical exercise in elite male orienteers. *Clin Physiol.* 1998;18:498-503.

37. Henriksen E, Landelius J, Kangro T, et al. An echocardiographic study of right and left ventricular adaptation to physical exercise in elite female orienteers. *Eur Heart J.* 1999;20:309-316.

38. D'Andrea A, Riegler L, Golia E, et al. Range of right heart measurements in top-level athletes: The training impact. *Int J Cardiol.* 2011.

39. Scharhag J, Schneider G, Urhausen A, Rochette V, Kramann B, Kindermann W. Athlete's heart: right and left ventricular mass and function in male endurance athletes and untrained individuals

determined by magnetic resonance imaging. *J Am Coll Cardiol.* 2002;40:1856-1863.

40. Abinader EG, Sharif D, Sagiv M, Goldhammer E. The effects of isometric stress on left ventricular filling in athletes with isometric or isotonic training compared to hypertensive and normal controls. *Eur Heart J.* 1996;17:457-461.

41. Basavarajaiah S, Makan J, Naghavi SH, Whyte G, Gati S, Sharma S. Physiological upper limits of left atrial diameter in highly trained adolescent athletes. *J Am Coll Cardiol.* 2006;47:2341-2; author reply 2342.

42. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol.* 2003;42:1687-1713.

43. Stein R, Medeiros CM, Rosito GA, Zimerman LI, Ribeiro JP. Intrinsic sinus and atrioventricular node electrophysiologic adaptations in endurance athletes. *J Am Coll Cardiol.* 2002;39:1033-1038.

44. Ryan MP, Cleland JG, French JA, et al. The standard electrocardiogram as a screening test for hypertrophic cardiomyopathy. *Am J Cardiol.* 1995;76:689-694.

45. Marcus FI. Prevalence of T-wave inversion beyond V1 in young normal individuals and usefulness for the diagnosis of arrhythmogenic

right ventricular cardiomyopathy/dysplasia. *Am J Cardiol.* 2005;95:1070-1071.

46. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol.* 1992;20:1391-1396.

47. Basavarajaiah S, Wilson M, Whyte G, Shah A, Behr E, Sharma S. Prevalence and significance of an isolated long QT interval in elite athletes. *Eur Heart J.* 2007;28:2944-2949.

48. Stolt A, Karila T, Viitasalo M, Mantysaari M, Kujala UM, Karjalainen J. QT interval and QT dispersion in endurance athletes and in power athletes using large doses of anabolic steroids. *Am J Cardiol.* 1999;84:364-6, A9.

49. Papadakis M, Basavarajaiah S, Rawlins J, et al. Prevalence and significance of T-wave inversions in predominantly Caucasian adolescent athletes. *Eur Heart J.* 2009;30:1728-1735.

50. Wasserburger RH. Observations on the juvenile pattern of adult negro males. *Am J Med.* 1955;18:428-437.

51. Littmann D. Persistence of the juvenile pattern in the precordial leads of healthy Negroes, with report of electrocardiographic survey in 300 Negroes and 200 white subjects. . *Am Heart J.* 1946;32.

52. Walker AR, Walker BF. The bearing of race, sex, age, and nutritional state on the precordial electrocardiograms of young South African Bantu and Caucasian subjects. *Am Heart J.* 1969;77:441-459.

53. Balady GJ, Cadigan JB, Ryan TJ. Electrocardiogram of the athlete: an analysis of 289 professional football players. *Am J Cardiol.* 1984;53:1339-1343.

54. Choo JK, Abernethy WB3, Hutter AMJ. Electrocardiographic observations in professional football players. *Am J Cardiol.* 2002;90:198-200.

55. Yesalis CS WJ. History of anabolic steroid use in Sports and exercise.. In: Yesalis Y, eds. *Anabolic Steroids in Sports and Exercise.* Human Kinetics; 2000:489.

56. Bjørnstad H, Storstein L, Meen HD, Hals O. Electrocardiographic findings of repolarization in athletic students and control subjects. *Cardiology.* 1994;84:51-60.

57. Pelliccia A, Culasso F, Di Paolo FM, et al. Prevalence of abnormal electrocardiograms in a large, unselected population undergoing pre-participation cardiovascular screening. *Eur Heart J.* 2007;28:2006-2010.

58. Sofi F, Capalbo A, Pucci N, et al. Cardiovascular evaluation, including resting and exercise electrocardiography, before participation in competitive sports: cross sectional study. *BMJ.* 2008;337:a346.

59. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation.* 2009;119:1085-1092.

60. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2011.

61. Maron BJ, Peterson EE, Maron MS, Peterson JE. Prevalence of hypertrophic cardiomyopathy in an outpatient population referred for echocardiographic study. *Am J Cardiol.* 1994;73:577-580.

62. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation.* 1995;92:785-789.

63. Maron BJ, Carney KP, Lever HM, et al. Relationship of race to sudden cardiac death in competitive athletes with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2003;41:974-980.

64. Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two-dimensional echocardiographic study. *J Am Coll Cardiol.* 1983;2:437-444.

65. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med.* 1997;336:775-785.

66. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation.* 2006;114:2232-2239.

67. Lewis JF, Spirito P, Pelliccia A, Maron BJ. Usefulness of Doppler echocardiographic assessment of diastolic filling in distinguishing "athlete's heart" from hypertrophic cardiomyopathy. *Br Heart J.* 1992;68:296-300.

68. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed

Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1987;10:733-742.

69. Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation.* 2001;104:128-130.

70. Nagueh SF, McFalls J, Meyer D, et al. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with subclinical disease. *Circulation.* 2003;108:395-398.

71. Palka P, Lange A, Fleming AD, et al. Differences in myocardial velocity gradient measured throughout the cardiac cycle in patients with hypertrophic cardiomyopathy, athletes and patients with left ventricular hypertrophy due to hypertension. *J Am Coll Cardiol.* 1997;30:760-768.

72. Ha JW, Ahn JA, Kim JM, et al. Abnormal longitudinal myocardial functional reserve assessed by exercise tissue Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr.* 2006;19:1314-1319.

73. Sharma S, Elliott PM, Whyte G, et al. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. *J Am Coll Cardiol.* 2000;36:864-870.

74. Moon JC, Fisher NG, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. *Heart.* 2004;90:645-649.

75. Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. *J Am Coll Cardiol.* 2003;41:1561-1567.

76. Harmon KG, Asif IM, Klossner D, Drezner JA. Incidence of sudden cardiac death in national collegiate athletic association athletes. *Circulation.* 2011;123:1594-1600.

77. Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation.* 2007;115:1643-1455.

78. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA.* 2002;287:1308-1320.

79. Marcus FI. Electrocardiographic features of inherited diseases that predispose to the development of cardiac arrhythmias, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy/dysplasia, and Brugada syndrome. *J Electrocardiol.* 2000;33 Suppl:1-10.

80. Wikipedia. List of the 2008 summer Olympic medal Winners.

81. Acosta, Ca. *Women in Intercollegiate sport: A lonigutdinal study 29 year update 1977-2006.* ; 2006.

82. Irwin CC, Irwin RL, Ryan TD, Drayer J. Urban minority youth swimming (in)ability in the United States and associated demographic characteristics: toward a drowning prevention plan. *Inj Prev.* 2009;15:234-239.

83. Wilson MG, Basavarajaiah S, Whyte GP, Cox S, Loosemore M, Sharma S. Efficacy of personal symptom and family history questionnaires when screening for inherited cardiac pathologies: the role of electrocardiography. *Br J Sports Med.* 2008;42:207-211.

84. Dubois DDE. Clinical calorimetry. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med.* 1916;17:863-871.

85. Bhopal R. Glossary of terms relating to ethnicity and race: for reflection and debate. *J Epidemiol Community Health.* 2004;58:441-445.

86. Agyemang C, Bhopal R, Bruijnzeels M. Negro, Black, Black African, African Caribbean, African American or what? Labelling African origin populations in the health arena in the 21st century. *J Epidemiol Community Health.* 2005;59:1014-1018.

87. Freidmann HH. *Diagnostic Electrocardiography and Vectorcardiography.* New York: McGraw-Hill; 1971.

88. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J.* 1949;37:161-186.

89. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7:79-108.

90. Devereux RB. Detection of left ventricular hypertrophy by M-mode echocardiography. Anatomic validation, standardization, and comparison to other methods. *Hypertension.* 1987;9:II19-II26.

91. Otterstad JE, Froeland G, St John Sutton M, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic

measurements of left ventricular dimensions and function. *Eur Heart J.* 1997;18:507-513.

92. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. *Ann Clin Res.* 1971;3:323-332.

93. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. *Circulation.* 1990;82:1995-2002.

94. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol.* 2003;42:873-879.

95. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *Am Heart J.* 2004;147:218-223.

96. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol.* 2002;90:29-34.

97. Klues HG, Roberts WC, Maron BJ. Morphological determinants of echocardiographic patterns of mitral valve systolic anterior motion in obstructive hypertrophic cardiomyopathy. *Circulation.* 1993;87:1570-1579.

98. Leonardi S, Raineri C, De Ferrari GM, et al. Usefulness of cardiac magnetic resonance in assessing the risk of ventricular arrhythmias and

sudden death in patients with hypertrophic cardiomyopathy. *Eur Heart J.* 2009;30:2003-2010.

99. Sen-Chowdhry S, Prasad SK, Syrris P, et al. Cardiovascular magnetic resonance in arrhythmogenic right ventricular cardiomyopathy revisited: comparison with task force criteria and genotype. *J Am Coll Cardiol.* 2006;48:2132-2140.

100. Vitelli LL, Crow RS, Shahar E, Hutchinson RG, Rautaharju PM, Folsom AR. Electrocardiographic findings in a healthy biracial population. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Am J Cardiol.* 1998;81:453-459.

101. Rautaharju PM, Zhou SH, Calhoun HP. Ethnic differences in ECG amplitudes in North American white, black, and Hispanic men and women. Effect of obesity and age. *J Electrocardiol.* 1994;27 Suppl: 20-31.

102. Xie X, Liu K, Stamler J, Stamler R. Ethnic differences in electrocardiographic left ventricular hypertrophy in young and middle-aged employed American men. *Am J Cardiol.* 1994;73:564-567.

103. Vitelli LL, Crow RS, Shahar E, Hutchinson RG, Rautaharju PM, Folsom AR. Electrocardiographic findings in a healthy biracial population. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Am J Cardiol.* 1998;81:453-459.

104. Katona PG, McLean M, Dighton DH, Guz A. Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest. *J Appl Physiol.* 1982;52:1652-1657.

105. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force

of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J.* 1994;71:215-218.

106. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation.* 2010;121:1533-1541.

107. Rawlins J, Mills P, Sharma S. ECG Repolarization abnormalities in an African Descent Athlete: Pathologic or Physiologic Finding? In: *Sports Cardiology Casebook.* Springer; 2009:85-91.

108. Pelliccia A, Di Paolo FM, Quattrini FM, et al. Outcomes in athletes with marked ECG repolarization abnormalities. *N Engl J Med.* 2008;358:152-161.

109. Eckart RE, Scoville SL, Shry EA, Potter RN, Tedrow U. Causes of sudden death in young female military recruits. *Am J Cardiol.* 2006;97:1756-1758.

110. Papadakis M, Sharma S. Electrocardiographic screening in athletes: the time is now for universal screening. *Br J Sports Med.* 2009;43:663-668.

111. Rickers C, Wilke NM, Jerosch-Herold M, et al. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. *Circulation.* 2005;112:855-861.

112. Charron P, Arad M, Arbustini E, et al. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2010;31:2715-2726.

113. Slama M, Susic D, Varagic J, Frohlich ED. Diastolic dysfunction in hypertension. *Curr Opin Cardiol.* 2002;17:368-373.

114. Kingwell B, Boutouyrie P. Genetic influences on the arterial wall. *Clin Exp Pharmacol Physiol.* 2007;34:652-657.

115. Mulukutla SR, Venkitachalam L, Bambs C, et al. Black race is associated with digital artery endothelial dysfunction: results from the Heart SCORE study. *Eur Heart J.* 2010;31:2808-2815.

116. Kalinowski L, Dobrucki IT, Malinski T. Race-specific differences in endothelial function: predisposition of African Americans to vascular diseases. *Circulation.* 2004;109:2511-2517.

117. Barley J, Blackwood A, Miller M, et al. Angiotensin converting enzyme gene I/D polymorphism, blood pressure and the renin-angiotensin system in Caucasian and Afro-Caribbean peoples. *J Hum Hypertens.* 1996;10:31-35.

118. Nguyen QM, Srinivasan SR, Xu JH, Chen W, Berenson GS. Racial (black-white) divergence in the association between adiponectin and arterial stiffness in asymptomatic young adults: the Bogalusa heart study. *Am J Hypertens.* 2008;21:553-557.

119. DeBosch B, Treskov I, Lupu TS, et al. Akt1 is required for physiological cardiac growth. *Circulation.* 2006;113:2097-2104.

120. Pauliks LB, Cole KE, Mergner WJ. Increased insulin-like growth factor-1 protein in human left ventricular hypertrophy. *Exp Mol Pathol.* 1999;66:53-58.

121. Schluter KD, Goldberg Y, Taimor G, Schafer M, Piper HM. Role of phosphatidylinositol 3-kinase activation in the hypertrophic growth of adult ventricular cardiomyocytes. *Cardiovasc Res.* 1998;40:174-181.

122. Seriki O, Smith AJ. The electrocardiogram of young Nigerians. *Am Heart J.* 1966;72:153-157.

123. Burke A, Creighton W, Mont E, et al. Role of SCN5A Y1102 polymorphism in sudden cardiac death in blacks. *Circulation.* 2005;112:798-802.

124. Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. *Heart Rhythm.* 2004;1:600-607.

125. Minson CT, Halliwill JR, Young TM, Joyner MJ. Influence of the menstrual cycle on sympathetic activity, baroreflex sensitivity, and vascular transduction in young women. *Circulation.* 2000;101:862-868.

126. Minson CT, Halliwill JR, Young TM, Joyner MJ. Sympathetic activity and baroreflex sensitivity in young women taking oral contraceptives. *Circulation.* 2000;102:1473-1476.

127. Payne JR, Kotwinski PJ, Montgomery HE. Cardiac effects of anabolic steroids. *Heart.* 2004;90:473-475.

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Publications And Prizes

Original Articles:

J. Rawlins, F. Carre, G. Kervio, M. Papadakis, N. Chandra, C. Edwards, G.P. Whyte, and S. Sharma. Ethnic Differences in Physiological Cardiac Adaptation to Intense Physical Exercise in Highly Trained Female Athletes. Circulation 2010;121 1078-1085 (Appendix D)

J Rawlins, A Bhan, S Sharma. Left Ventricular Hypertrophy in Athletes. Eur J Echo 2009 (10),350-356 (Appendix E)

Papadakis M, Carre F, Kervio G, **Rawlins J,** Panoulas VF, Chandra N, Basavarajaiah S, Carby L, Fonseca T, Sharma S. The prevalence, distribution and clinical outcomes of electrocardiographic repolarization patterns in male athletes of Afro-Caribbean origin. Eur Heart J, 2011 Sep;32(18):2304-13 (Appendix F)

Papadakis M, Basavarajaiah S, **Rawlins J**, Edwards C, Makan J, Firoozi S, Carby L, Sharma S. Prevelance and significance of T-wave inversions in predominantly Caucasian adolescent athletes. Eur H J 2009. Jul;30(14):1728-35 (Appendix G)

Educational Material – Chapters

John Rawlins, William McKenna, Sanjay Sharma. Electrocardiographic Manifestations of the Athletes Heart and Management of Arrhythmia's in the Athlete. Chapter 53. Electrophysiological Disorders of the Heart. Ed. Saksena & Camm, Pub Elsevier, 2011

John Rawlins, Peter Mills, Sanjay Sharma. Chapter 13 ECG Repolarization Abnormalities in an African Descent Athlete:Pathologic or Physiologic Finding? Cases in Sports Cardiology. Ed: A Pelliccia. Springer 2009

Oral Abstracts

J Rawlins, Dr F Carre, Dr M Papadakis, Dr N Chandra, Dr C Edwards, Dr S Sharma. Ethnic Differences in Physiological Cardiac Adaptation to Intense Physical Exercise in Highly Trained Female Athletes. Eur J Cardio Prevent & Rehab 2009. Suppl I S121. Abstract N#O578 – Young Investigator Award

J Rawlins, M Papadakis, C Edwards, S Basavarajah, S Sharma. Ethnic differences in the 12-Lead EKG – Relevance to the Cardiovascular Evaluation for Hypertrophic Cardiomyopathy in Athletes. Circulation 2008 Suppl (II) 118;18: S1121. Oral Presentation AHA 2008

JC. Rawlins, C. Edwards, M. Papadakis, S. Sharma. Gender differences in electrocardiographic appearances of the athlete's heart in relation to pre-participation screening for hypertrophic cardiomyopathy. Eur H J 2008 Suppl (I) 29: S261 Abstract N# 83751. Oral Presentation ESC Congress 2008, Munich

JC Rawlins, M Papadakis, C Edwards, S Gati, S Basavarajah, S Sharma. T wave inversions in Adolescent Athletes electrocardiograms: Prevalence and significance? Eur J Cardio Prevent & Rehab 2008; Suppl (1): S72. Oral Presentation Europrevent 2008

Moderated Posters

J Rawlins, F Carre, M Papadakis, N Chandra, A Kouloubinis, C Edwards, S Sharma : Normal Distribution of Left Ventricular Wall Thickness in Highly Trained Black Athletes. Abstract 878. Circulation, Nov 2009; 120: S41

J C. Rawlins, F. Carre, M. Papdakis, N. Chandra, C. Edwards, S. Sharma. The impact of race on electrocardiographic repolarisation changes in highly trained female athletes: relevance to pre-participation ECG screening for cardiomyopathy. ESC Congress 2009, Barcelona

J Rawlins, Dr F Carre, Dr M Papadakis, Dr N Chandra, Dr C Edwards, Dr S Sharma. Ethnic Differences in Physiological Cardiac Adaptation to Intense Physical Exercise in Highly Trained Female Athletes. Moderated poster BCS 2009. Heart 2009;95;120

Prizes –

Young Investigator Award – European Society of Cardiovascular Prevention and Rehabilitation**,** awarded at EuroPrevent 2009, Stockholm.

Appendix A - Screening Information for study participants

CRY

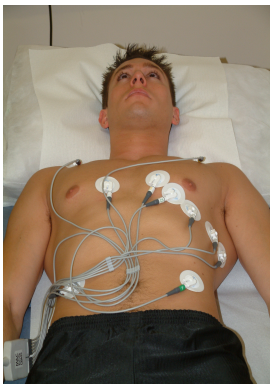
CARDIAC RISK IN THE YOUNG

Unit 7, Epsom Downs Metro Centre, Waterfield, Tadworth, Surrey, KT20 5LR United Kingdom
Telephone: +44(0) 01737 363 222 Facsimile +44(0) 01737 363 444
e-mail cry@c-r-y.org.uk web site www.c-r-y.org.uk

Cardiac Testing – Who are CRY and why is cardiac testing important?

CRY are a charity-based organisation whose mission is to raise awareness of undetected cardiac abnormalities in young, apparently healthy individuals. Although governmental statistics are not available, cardiac experts believe that 4-8 young people die each week in the UK from undiagnosed cardiac conditions. It is important to stress that the majority of these deaths **ARE** preventable. It is also important to realise that exercise is **NOT** bad for you, but can act as a trigger for an event if the individual already has underlying heart condition.

Individuals may be tested from the age of 14 until 35. Individuals may make a special request (subject to approval) to be screened before their 14th birthday. The reason being that growth changes during puberty will alter results year by year and make valid documentation difficult. Tests performed on pre-pubescent teenagers should be repeated at a later date.



An Electrocardiogram (or ECG for short) is a simple, non-invasive and painless electrical test that examines the electrical activity within your heart. As you can see from the picture on the left, the ECG involves the patient lying down quietly for 5-10 minutes only. You should have rested for at least 30 minutes prior to your ECG.

Small stickers (known as electrodes) are placed at strategic points on your chest. Flexible leads that extend from the ECG machine are then attached to these stickers. The electrical rhythm of your heart is recorded and printed out on thermal paper. This part of the process only takes 2-3 minutes to perform and after that you are free to go. As you can see from the picture, the technician will have to access your bare chest. Female technicians are used where possible for female patients, and the ECG can be obtained whilst wearing a non-wired sports bra.

In addition to this, you will undergo an Echocardiogram (ECHO) whilst lying down. It is an ultrasound scan of the heart that measures cardiac dimensions and the flow of the blood in and out of the heart. Just like a sonogram of a pregnant woman, the scan is painless, non-invasive and takes no more than 20 minutes. Please note that all our technicians work as ECG/ECHO technicians within the NHS or BUPA, and furthermore, all our technicians have been investigated by the Criminal Records Bureau and are free to work for CRY.

CRY

CARDIAC RISK IN THE YOUNG

Unit 7, Epsom Downs Metro Centre, Waterfield, Tadworth, Surrey, KT20 5LR United Kingdom
Telephone: +44(0) 01737 363 222 Facsimile +44(0) 01737 363 444
e-mail cry@c-r-y.org.uk web site www.c-r-y.org.uk

After the ECG and ECHO have taken place, the results are taken to our consultant cardiologist, whose speciality is cardiac adaptation in athletic individuals. The consultant reviews each individual with the personal and family history questionnaire you would have completed prior to examination. It is extremely important that you fill in these questionnaires to the best of you ability. Do not guess on history you don't know, instead ask a family member to fill in the missing gaps.

In the majority to cases, patients will receive an "all clear" letter, but sometimes patients will be invited to attend University Hospital Lewisham or the CRY Centre for Sports Cardiology for further cardiac testing.

There are a number of reasons why follow up tests are felt to be of benefit. The ECG and ECHO readings taken during the testing **MAY** indicate an athlete's heart (enlarged heart muscle due to large volumes of physical activity), borderline measurements, or imperfect readings. In order to properly rule out a cardiac abnormality, a further ECG and ECHO may be required. Additional tests, such as a Holtor monitor (a 24 or 48 hour ECG) and/or exercise stress test may also be required. It is important to realise that a further review does not necessarily mean you have a cardiac condition. However, further information is required to give a full diagnostic evaluation.

The information derived from these tests are strictly confidential and will not be disclosed to anyone other than your doctor or others who are directly involved within your care, e.g. other consultant cardiologists. In the rare event that a cardiac abnormality is diagnosed you must be aware that this may affect certain mortgage applications, particular types of life insurance and some careers. CRY have a comprehensive

resource network for affected individuals and family members that includes counselling and personal advice.

It must be stressed that undetected heart conditions are rare. Our tests are able to detect the majority of cardiac abnormalities most likely to affect young people. In order for you to have an ECG and ECHO, you must have fully read the information provided. If you are unsure about anything, please visit our website at: www.c-r-y.org.uk for more information. If you still can't find the information you are looking for, please contact the CRY office and one of us will endeavour to give you the answer.

CRY Health Questionnaires and Consent Forms will be distributed with this information letter, but it should be noted that young people wishing to be tested, who are under the age of sixteen, must seek written permission from a parent or guardian.

Appendix B - Consent form for study participants

CRY CARDIAC RISK IN THE YOUNG

CRY, Unit 7, Epsom Downs Metro Centre, Waterfield, Tadworth, Surrey KT20 5LR U.K.
Tel: 01737 363 222 Fax: 01737 363 444 e-mail cry@c-r-y.org.uk web site www.c-r-y.org.uk

Consent Form for Cardiac Screening

It is extremely important that you have read and understood the information sheet provided with this consent form

☐Please tick the following box to confirm you have fully read and understood the screening information on the attached.

Test Procedure: An Electrocardiogram (or ECG for short) is a simple, non-invasive and painless test that examines the electrical activity within your heart. Small stickers are placed at strategic points on your chest. Flexible leads that extend from the ECG machine are then attached to these stickers. The electrical rhythm of your heart is recorded and printed out on thermal paper. Female technicians are used where possible for female patients. If you wish, a friend or chaperone can accompany you during the procedures. All medical personnel who are linked to CRY are verified and approved by Dr Sanjay Sharma and/or Professor WJ McKenna. All results are treated in the strictest of confidence.

Results: It should be noted that the ECG will appear abnormal in a small percentage of cases and clients will require follow up tests to further evaluate cardiac health. In some cases you may be requested to have an echocardiogram to facilitate the interpretation of the ECG. Echocardiograms are not carried out routinely for all clients but only when felt warranted on the basis of initial ECG findings or alternatively for research purposes. This may be on the same day as the ECG testing or at a later date. CRY aims to notify you (or your parents if you are under 16) and your GP within 4 working weeks after the screening event.

.....

STATEMENT: I have read and understood the implications of further testing, outlined in the CRY Information Sheet. I understand that in the rare event an abnormality is confirmed, this may affect some types of mortgage and health insurance applications and that it may also affect some careers. Questions concerning the testing procedure have been answered to my satisfaction. I also understand that I am free to withdraw consent and discontinue participating in any procedures without giving a reason. I have also been informed that the information derived from these tests is confidential and will not be disclosed to anyone other than my doctor or others who are involved within my care. However, I do agree that the information from these tests will be held on a database at CRY and can be used anonymously for research purposes.

(SIGNATURE)

.....

NAME OF CLIENT (PRINTED)……...
……...

CONTACT TEL. NO. ……
……..

PARENTS SIGNATURE……
DATE……
(Required if individual is under 16 years of age)

Appendix C - Screening questionnaire

Full Name *(Include parents names if under 16)*:	**Date of Screening**:

Personal Details

Home *(correspondence)* address: Phone Number:			Doctors name and Address: Phone Number
Date of Birth:	Age:	Gender:	Main Sport(s):
Height:			Weight:
Have you been screened before?			If so, when and where?
Are you taking any medication:			If so, please describe?

Ethnicity *(please tick the appropriate box)*

White	**Mixed**	**Black**	**Asian**	**Other**
British ☐	White and Black Caribbean ☐	Caribbean ☐	Indian ☐	Chinese ☐
Irish ☐	White and Black African ☐	East African ☐	Pakistani ☐	Filipino ☐
Turkish / Cypriot ☐	White and Asian ☐	West African ☐	Bangladeshi ☐	Vietnamese ☐
Greek / Cypriot ☐				
Kurdish ☐				
Other ☐	Other Mixed ☐	Other ☐	Other ☐	Any other ethnic group ☐
If other, please state your ethnic origin:				

For Office Use Only			
Payment Received:	Questionnaire Checked:	Info box ticked:	Consent Signed:
Seen By Doctor:	Follow-up Required: Yes		No
Additional Notes: Result:			

Height ……cm Weight……Kg Blood Pressure……/ …..mmHg

Name:

1. Have you ever fainted?

During Exercise	Yes / No	How recently did this occur?	Please describe the circumstances:
Following Exercise	Yes / No	How recently did this occur?	Please describe the circumstances:
Unrelated to exercise	Yes / No	How recently did this occur?	Please describe the circumstances:

2. Do you experience dizzy turns?

During Exercise	Yes / No	How recently did this occur?	Please describe the circumstances:
Following Exercise	Yes / No	How recently did this occur?	Please describe the circumstances:
Unrelated to exercise	Yes / No	How recently did this occur?	Please describe the circumstances:

3. Do you experience palpitations? *(palpitations are a fluttering in your chest that you can notice whilst resting)*

Yes / No	If yes, how recently and please describe the circumstances

4. Do you experience chest pain, heaviness or tightness?

During Exercise	Yes / No	If yes, please describe the circumstances
Following Exercise	Yes / No	
Unrelated to exercise	Yes / No	

5. Do you feel that you are more breathless or more easily tired than your team mates?

Yes / No	If yes, please describe the circumstances

6. Is there a family history of (please tick):

High Blood pressure ☐ High Cholesterol ☐ Diabetes ☐

7. Is there a family history of heart disease?

Yes / No	If yes, please state the age of onset

8. Has there been an unexplained death or deaths due to heart disease in young family members?

Yes / No	If yes, please describe the circumstances and at what age did the death occur

What sports do you play and at what level?

e.g. International, National, County, Club, Other

A. …….. Level: …….

B. …….. Level: …….

C. …….. Level: …….

What would you consider your main sport?

Approximately, how many days a week are you physically active (playing sport)?

On average, approximately how many hours per week are you physically active (playing sport)?

Do you do any other training, e.g. weights, aerobics, circuit training etc?

If so, how often do you do these?

Appendix D -

Exercise Physiology

Ethnic Differences in Physiological Cardiac Adaptation to Intense Physical Exercise in Highly Trained Female Athletes

J. Rawlins, MRCP; F. Carre, PhD; G. Kervio, PhD; M. Papadakis, MRCP; N. Chandra, MRCP; C. Edwards, MRCP; G.P. Whyte, PhD; S. Sharma, MD

Background—Ethnicity is an important determinant of cardiovascular adaptation in athletes. Studies in black male athletes reveal a higher prevalence of electric repolarization and left ventricular hypertrophy than observed in white males; these frequently overlap with those observed in cardiomyopathy and have important implications in the preparticipation cardiac screening era. There are no reports on cardiac adaptation in highly trained black females, who comprise an increasing population of elite competitors.

Methods and Results—Between 2004 and 2009, 240 nationally ranked black female athletes (mean age 21±4.6 years old) underwent 12-lead ECG and 2-dimensional echocardiography. The results were compared with 200 white female athletes of similar age and size participating in similar sports. Black athletes demonstrated greater left ventricular wall thickness (9.2±1.2 versus 8.6±1.2 mm, $P<0.001$) and left ventricular mass (187.2±42 versus 172.3±42 g, $P=0.008$) than white athletes. Eight black athletes (3%) exhibited a left ventricular wall thickness >11 mm (12 to 13 mm) compared with none of the white athletes. All athletes revealed normal indices of systolic and diastolic function. Black athletes exhibited a higher prevalence of T-wave inversions (14% versus 2%, $P<0.001$) and ST-segment elevation (11% versus 1%, $P<0.001$) than white athletes. Deep T-wave inversions (−0.2 mV) were observed only in black athletes and were confined to the anterior leads (V_1 through V_3).

Conclusions—Systematic physical exercise in black female athletes is associated with greater left ventricular hypertrophy and higher prevalence of repolarization changes than in white female athletes of similar age and size participating in identical sporting disciplines. However, a maximal left ventricular wall thickness >13 mm or deep T-wave inversions in the inferior and lateral leads are rare and warrant further investigation. **(*Circulation*. 2010;121:1078-1085.)**

Key Words: ethnicity ■ echocardiography ■ electrocardiography ■ women ■ hypertrophy ■ exercise

Regular participation in intense sporting activity is associated with physiological electric, structural, and functional cardiac modifications[1] that frequently manifest on the ECG,[2,3] 2-dimensional echocardiogram,[4–6] and exercise stress test.[7] The magnitude of such adaptations is largely determined by demographic factors and sporting discipline.[2–6] Generally, extreme manifestations of the athlete's heart are confined to adult males participating in endurance sporting disciplines; in rare instances, these overlap with manifestations observed in individuals with hypertrophic cardiomyopathy (HCM).[4] In contrast, white female athletes do not exhibit ECG or echocardiographic changes that may be regarded as representing HCM.[8,9]

Editorial see p 1066
Clinical Perspective on p 1085

There is increasing evidence that an athlete's ethnic origin may have a significant impact on the cardiovascular response to exercise. Recent studies examining cardiac adaptation in African/Afro-Caribbean (black) male athletes demonstrated that black male athletes develop more striking repolarization changes on the ECG and exhibit a greater magnitude of left ventricular hypertrophy (LVH) than white male athletes of similar age and size participating in identical sports.[10,11] Indeed, up to 25% of black athletes exhibit either repolarization changes or LVH that overlaps with morphologically mild HCM.[11] These observations are relevant to recent recommendations attempting to mandate cardiovascular screening among elite sportsmen, particularly in countries such as the United States and the United Kingdom, where black athletes represent a substantial fraction of athletes competing at the national level.

Current standardized ECG guidelines that are used to differentiate between a normal ECG and one that is potentially indicative of cardiac pathology are derived from the white athletic population and raise the potential for false

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diagnoses and unnecessary disqualification in black athletes.[12,13] There are no data relating to cardiovascular adaptation in black female athletes, who comprise an increasing proportion of athletes representing Western countries at international sporting events. However, this unstudied group may potentially be subject to similar issues as black male athletes. The aim of the present study was to examine the ECG and echocardiographic appearances in highly trained national-level black female athletes to facilitate clinical decisions relating to future preparticipation cardiovascular screening.

Methods

Setting

The study was part of a collaborative research program between the United Kingdom and France since 2006 to characterize cardiovascular adaptation in black athletes. Neither country has a nationally sponsored cardiovascular screening program for athletes; however, in the United Kingdom, certain sporting bodies, including the International Olympic Committee,[13] football associations (Union of European Football Associations, Fédération Internationale de Football),[14] Lawn Tennis Association, and the International Rugby Board, have privately funded mandatory screening for all athletes competing at the national level.

Athletes not affiliated with these organizations but participating in the Commonwealth Games also undergo mandatory preparticipation screening. Most UK screenings are supervised by the senior author (SS) at national sporting training camps, the Olympic Medical Institute, King's College Hospital, and University Hospital Lewisham. In France, all athletes participating at the national level undergo mandatory preparticipation cardiovascular screening; the majority of screenings are supervised by the second author (FC) at the University of Rennes.

Subjects

Between 2006 and 2009, 440 consecutive nationally ranked female athletes (240 [55%] black) underwent assessment with a health questionnaire, physical examination, ECG, and 2-dimensional echocardiography as part of a standard preparticipation cardiac evaluation. All athletes provided written consent for the evaluation. Ethics approval was obtained from the University Hospital Lewisham Research Ethics Committee. Black ethnicity was determined through self-reported questionnaires that included terms such as black African, black Afro-Caribbean, black British, and black French.

Twelve-Lead ECG

A standard ECG was performed with the subject in a supine position with a Philips Pagewriter Trim III (Philips, Bothell, Wash) recorder as described previously.[15] Heart rate and QRS axis were calculated. P-, Q-, R-, S-, and T-wave voltages; ST segments; QRS duration; PR interval; and QT interval were measured in each lead with calipers. The QT interval was corrected for the heart rate by use of the Bazett formula.[16] Electrocardiographic LVH was defined with the Sokolow-Lyon voltage criterion.[17] T-wave inversions in 2 or more contiguous leads were considered significant, other than in leads V_1 and III.

Transthoracic Echocardiography

A 2-dimensional echocardiogram was conducted by 1 of 3 experienced cardiologists (including 2 authors: J.R. and G.K.) using GE Vivid I (General Electric, Tirat Carmel, Israel), Philips Sonos 7500, or Philips CPX50 cardiac ultrasound equipment. Standard views of the heart were obtained and analyzed according to the protocol specified by the European Society of Echocardiography.[18] Left ventricular (LV) wall thickness (LVWT) was measured in the 2-dimensional parasternal short axis, at the levels of the mitral valve and papillary muscles, the greatest measurement being defined as the maximal LVWT. LV mass (LVM) was calculated with the formula of Devereux.[19] LV ejection fraction was calculated from LV volumes by Simpson's rule.[20] Assessment of diastolic function included traditional pulsed-wave Doppler across the mitral valve[21] and tissue Doppler velocity imaging[22] of the septal and lateral mitral valve annulus. Echocardiographic studies were saved to compact discs as numeric files to generate anonymity, and cardiac measurements were repeated independently by an experienced cardiologist (S.S.) blinded as to the identity of the athlete.

Further Evaluation

Athletes with LVH (LVWT >11 mm) or deep (more than −0.2 mV) T-wave inversions in 2 contiguous leads were investigated further with an exercise test, 48-hour Holter monitor, and cardiac magnetic resonance scan to investigate the broader phenotypic features of HCM.

Exercise Stress Testing

An upright treadmill stress test was performed with the standard Bruce protocol.[23] ECGs and blood pressure (BP) were recorded at 1-minute intervals. Athletes were exercised to volitional exhaustion and assessed specifically for the development of ischemic changes, BP response,[24] and arrhythmias.

Forty-Eight-Hour ECG Monitoring

Forty-eight-hour ambulatory ECG monitoring was performed to check specifically for supraventricular and ventricular tachyarrhythmias.[25] Athletes were encouraged to continue daily activities, including exercise, during the investigation.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging was performed with a Siemens Sonata 1.5T system (Erlangen, Germany) with steady-state, free-precession breath-hold cines (time to echo/repetition time 1.6/3.2 ms, flip angle 60°) in long-axis planes and sequential 7-mm short-axis slices (3-mm gap) from the atrioventricular ring to the apex. Late gadolinium enhancement images were acquired 10 minutes after intravenous administration of gadolinium-DTPA (Schering, 0.1 mmol/kg) in identical short-axis planes with an inversion-recovery gradient echo sequence. Inversion times were adjusted to null normal myocardium (typically 320 to 440 ms; pixel size 1.7×1.4 mm). Late gadolinium enhancement images were phase-swapped to exclude artifact. Ventricular volumes and function were measured for both ventricles by standard techniques[26,27] and analyzed with semiautomated software (CMR tools, Cardiovascular Imaging Solutions, London, United Kingdom). All volumes and masses were indexed for age and body surface area.

Statistical Analysis

Data are expressed as mean±SD. Statistical analyses were performed with unpaired Student *t* test and Fisher exact test, calculated from a 2×2 contingency table.

For continuous variables, a stepwise multivariable linear regression model was constructed to assess the relationship between LVWT and LVM as dependent variables, with age, height, weight, body surface area, ethnicity, and hours trained as predictors. For binary variables, a binary logistic regression model was constructed to assess any relationship between T-wave inversions or ST-segment elevation as dependent variables and age, height, weight, body surface area, number of hours trained, ethnicity, maximal LVWT, and LV end-diastolic cavity diameter as independent variables. SPSS version 12 was used for all statistical analyses. $P<0.05$ was considered significant and was essential for predictors to enter and remain in multivariable regression models.

Results

Subjects

All athletes were asymptomatic and normotensive (BP ≤120/80 mm Hg), and none volunteered a family history of

Table 1. Demographics of Black and White Athletes

	Black Athletes (n=240)	White Athletes (n=200)	P
Age, y	21±4.6 (14, 35)	20±4.0 (14, 35)	0.18
Weight, kg	66.1±11.6 (39, 106)	64.1±8.8 (45, 92)	0.06
Height, m	1.71±8.4 (1.50, 1.92)	1.70±7.7 (1.50, 1.91)	0.07
BSA, m^2	1.78±0.17 (1.31, 2.21)	1.73±0.18 (1.33, 1.96)	0.10
Resting BP, mm Hg	110±19 (120, 80)	111±13 (120, 80)	0.80
Training h/wk	13.7±3.4 (8, 24)	14.4±6.1 (8, 36)	0.41
Sporting discipline, %			
Athletics*	25	23	0.58
Basketball	20	18	0.63
Football (soccer)	16	20	0.26
Netball	18	18	1.00
Martial arts	13	11	0.56
Other	8†	10‡	0.50
LDR	n=8	n=10	
Fencing	n=3	n=2	
Handball	n=3	n=2	
Weightlifting	n=3	n=2	
Hockey	n=2	n=4	

BSA indicates body surface area; LDR, long-distance running.
Data are expressed as mean±SD (limits).
*Track and field events.
†n=19.
‡n=20.

cardiomyopathy or premature sudden cardiac death. Athletes were of similar age and size and competed in a similar range of sporting disciplines. The majority of black athletes (n=169; 70%) and white athletes (n=140; 70%) were from the United Kingdom (Table 1).

LV Dimensions

Black athletes demonstrated a greater maximal LVWT than white athletes (9.2±1.2 versus 8.6±1.2 mm, $P<0.001$), which amounted to a 7% difference between the 2 groups (Table 2). Calculated LVM was also greater in black athletes than in white athletes (187.2±42 versus 172.3±42 g, $P=0.008$).

Black athletes also exhibited a greater left atrial diameter than white athletes (35.3±4.7 versus 32.5±4.8 mm, $P<0.001$). There were no differences between the ethnic groups with respect to LV cavity size and aortic root diameter. Twenty black athletes (8%) and 12 white athletes (6%) revealed an enlarged (>54 mm) LV end-diastolic cavity. All athletes had normal indices of systolic and diastolic function.

LVH in Female Athletes

The distribution of maximal LVWT is shown in Figure 1. None of the white athletes demonstrated a maximal LVWT of >11 mm. In contrast, 8 black athletes (3.3%) exhibited a maximal LVWT >11 mm (12 to 13 mm) and were considered to exhibit LVH. The demographic, echocardiographic, and ECG features of the 8 black athletes with LVH are shown in Table 3.

Table 2. Comparison of Echocardiographic Cardiac Dimensions Between Black and White Female Athletes

	Black Athletes (n=240)	White Athletes (n=200)	P
Ao, mm	27.2±2.9 (23, 38)	26.4±3.5 (17, 33)	0.21
LA, mm	35.3±4.7 (21, 41)	32.5±4.8 (25, 47)	<0.0001
LVED, mm	48.6±3.9 (39, 60)	48.2±3.5 (40, 62)	0.93
LVES, mm	27.3±4.0 (21, 44)	30.5±4.7 (20, 44)	0.47
IVSd, mm	9.0±1.3 (6, 13)	8.4±1.2 (6, 11)	<0.001
PTWD, mm	8.7±1.3 (6, 12)	8.4±1.2 (6, 11)	0.14
Max LVWT, mm	9.2±1.2 (6, 13)	8.6±1.2 (6, 11)	<0.001
LVM, g	187.2±42 (95, 322)	172.3±42 (86, 293)	0.008
E wave, m/s	0.89±0.2 (1.36, 0.6)	0.90±0.2 (1.33, 0.53)	0.49
A wave, m/s	0.41±0.1 (1.1, 0.2)	0.44±0.1 (0.9, 0.2)	0.076
E/A ratio	2.3±0.8 (5.5, 1.1)	2.2±0.8 (5.5, 1.1)	0.15
E′, m/s	0.22±0.03 (0.25, 0.13)	0.23±0.03 (0.28, 0.17)	0.40
A′, m/s	0.07±0.03 (0.16, 0.02)	0.06±0.03 (0.13, 0.03)	0.43
E:E′	4.41±0.71 (5.61, 2.30)	4.46±0.74 (5.55, 1.96)	0.39
EF, %	67±6.7 (41, 78)	66±6.9 (44, 76)	0.48

Ao indicates aortic annulus diameter; LA, left atrial diameter; LVED, LV end-diastolic diameter; LVES, LV end-systolic diameter; IVSd, maximal LV septal wall thickness in end diastole; PTWD, LV posterior wall thickness in end diastole; Max LVWT, maximal LVWT in end diastole; E wave, early diastolic mitral valve peak inflow velocity; A wave, late diastolic mitral valve inflow peak velocity; E′, early diastolic annular peak velocity (lateral mitral annulus); A′, late annular diastolic peak velocity (lateral mitral annulus); E:E′, ratio of peak early diastolic mitral inflow velocity to peak early diastolic mitral annular velocity; and EF, ejection fraction.
Data are expressed as mean±SD (limits).

The pattern of LVH in all of the black female athletes was homogeneous, with a difference of <2 mm between adjacent segments. All athletes with LVH exhibited a normal LV diastolic cavity size (Table 3). None of the athletes with LVH exhibited dynamic LV outflow obstruction.[28] There were no differences in age (21.5±1.9 versus 21.3±4.6 years, $P=0.92$), height (1.69±0.11 versus 1.72±0.09 m, $P=0.496$), weight (75±11 versus 67±10.9 kg, $P=0.12$), or body surface area (1.85±0.19 versus 1.79±0.17 m^2, $P=0.45$) between black athletes with LVH and those without.

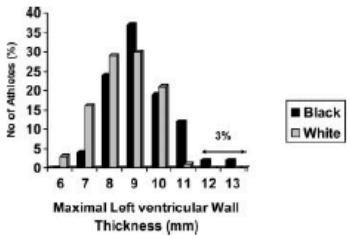

Figure 1. Histogram showing the distribution of maximal LVWT in black (black bars) and white (gray bars) female athletes. Three percent of black athletes demonstrated a maximal LVWT >11 mm compared with none of the white athletes.

Table 3. Demographic, Echocardiographic, and ECG Features of Black Athletes With LVH

Age, y	BSA, m^2	Sport	LVED, mm	LVES, mm	LAD, mm	MLVWT, mm	LVM, g	EF, %	E, m/s	A, m/s	E:A	E′, m/s	E:E′	T-Wave Inversion (Leads)	LAE	LVH
20	1.62	Judo	53	35	30	12	236	64	1.00	0.47	2.1	0.17	5.9	None	No	No
20	2.01	Netball	48	34	32	12	276	65	0.8	0.4	2	0.15	5.3	None	Yes	No
20	1.82	Sprinting	50	37	36	13	329	66	0.8	0.42	1.90	0.22	3.6	None	No	Yes
21	1.98	Basketball	51	37	36	13	260	68	0.8	0.39	2.1	0.16	5.0	None	No	No
22	1.71	Football	45	26	32	13	279	70	0.9	0.38	2.3	0.19	4.7	V_1, V_2	No	No
22	2.02	Netball	51	40	37	13	322	65	0.6	0.42	1.4	0.16	3.7	V_1, V_2	No	No
23	1.87	Football	48	33	31	12	276	67	0.72	0.41	1.8	0.21	3.4	None	No	Yes
24	1.77	Weightlifting	42	24	37	13	211	72	0.91	0.42	2.2	0.21	4.3	None	No	No

BSA indicates body surface area; LVED, LV end-diastolic diameter; LVES, LV end-systolic diameter; LAD, left atrial diameter; MLVWT=maximal LVWT; EF, ejection fraction; LAE, voltage criterion for left atrial enlargement; and LVH, voltage criterion for LVH.

Determinants of LVH

The results of a multivariable linear regression model that assessed the relationship between maximal LVWT and age, body surface area, ethnicity, and number of hours trained demonstrated that ethnicity was the strongest independent predictor of maximal LVWT (β=0.263, CI 0.29 to 0.855, P<0.001), with age being the only other significant factor (β=−0.155, CI −0.07 to 0.01, P=0.006). There was no relationship between sporting discipline and LVH.

Reliability of LVWT Measurements in Athletes

The averaged coefficients of variation between intraobserver and interobserver reliability for maximal LVWT measurements were 4% and 6.2%, respectively.

ECG Findings

Black athletes demonstrated a greater PR interval than white athletes, whereas white athletes revealed a slightly greater QRS duration than black athletes. There were no significant differences between black athletes and white athletes with respect to QRS axis, QT interval, voltage criteria for LVH, right or left atrial hypertrophy, or incomplete right bundle branch (Table 4). None of the athletes exhibited pathological Q waves (>40 ms wide or exceeding in depth 25% of the height of the preceding R wave), ST-segment depression, left bundle-branch block, or epsilon waves.

Repolarization Anomalies

Black athletes demonstrated a higher prevalence of ST-segment elevation than white athletes (n=26 [11%]) versus n=2 [1%]; P<0.001). Black athletes also exhibited a higher prevalence of contiguous T-wave inversions than white athletes (n=34 [14%]) versus n=4 [2%]; P<0.001; Figure 2). In black athletes, T-wave inversions were confined to leads V_1 through V_3 and exceeded −0.2 mV (deep T-wave inversions) in 6 individuals (2%; Figure 3D). In contrast, white athletes only showed T-wave inversions in leads III and aVF, and none exhibited deep T-wave inversions.

Determinants of Repolarization Anomalies

The results of a binary logistic regression model, with the dependent variable being the presence of T-wave inversions, demonstrated that black ethnicity was the only significant independent predictive factor (β=1.94, SE=0.417, P=0.003). Black ethnicity was also the strongest independent predictive factor (β=1.29, SE=349, P<0.001) when ST-segment elevation was used as a dependent variable in the model, with athlete height having a weak additional effect (β=0.042, SE=0.021, P=0.043).

Correlation Between ECG and Echocardiogram

There was a weak correlation between the presence of T-wave inversions and magnitude of LVWT and LVM in both groups (maximal LVWT: P=0.039; LVM: P=0.041). However, there were no significant differences in absolute values of maximal LVWT between athletes with T-wave inversions and those without in either group (black athletes: P=0.12; white athletes: P=0.07). The identification of T-wave inversions did not predict the presence of LVH or increased LV cavity size. There was no relationship between the presence of Sokolow-Lyon voltage criteria for LVH on the ECG and maximal LVWT or LVM (maximal LVWT: P=0.278; LVM: P=0.408).

Table 4. Comparison of ECG Parameters Between Black and White Female Athletes

	Black Athletes (n=240)	White Athletes (n=200)	P
Heart rate, bpm	61±8.3 (44, 85)	60±9.5 (35, 85)	0.26
PR interval, ms	162±25 (112, 246)	149±23 (88, 228)	<0.001
QRS duration, ms	84±10 (43, 105)	87±10 (66, 120)	0.0072
QT interval, ms	400±32 (330, 475)	415±33 (290, 447)	0.17
QTc (Bazett's), ms	404±42 (358, 465)	407±41 (285, 474)	0.28
Axis, degrees	67±14 (32, 89)	65±32 (−26, 129)	0.66
LAE, %	12.5	10	0.45
RAE, %	5	4	0.65
LVH voltage, %	8	12	0.16
Partial RBBB, %	14	14	0.89

QTc indicates corrected QT interval; LAE, voltage criterion for left atrial enlargement; RAE, voltage criterion for right atrial enlargement; and RBBB, right bundle-branch block.

Data are expressed as mean±SD (limits) or percentages, as appropriate.

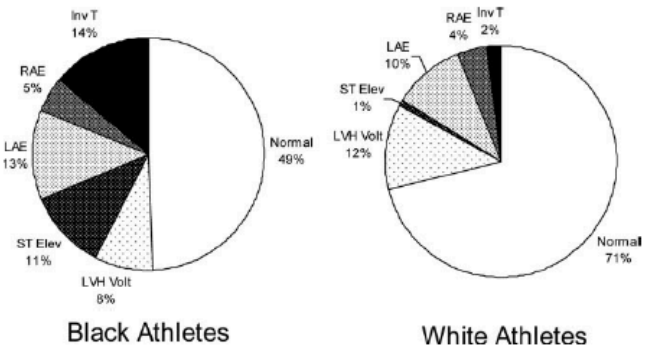

Figure 2. Pie charts comparing ECG anomalies between black athletes and white athletes. Black athletes exhibited a higher prevalence of ST-segment elevation and T-wave inversions than white athletes. LAE indicates voltage criterion for left atrial enlargement; RAE, voltage criterion for right atrial enlargement; LVH volt, voltage criterion for LVH; ST Elev, ST-segment elevation; and Inv T, T-wave inversion.

Subsequent Investigations

Twelve black athletes (exhibiting LVH and/or deep T-wave inversions) underwent an exercise stress test, 48-hour Holter monitoring, and a cardiac magnetic resonance scan. None of the 12 athletes demonstrated any phenotypic features of HCM or any other form of cardiomyopathy. Specifically, none of the 12 athletes exhibited flat BP responses to exercise,[24] >1000 ventricular extrasystoles/nonsustained ventricular tachycardia,[25] or late gadolinium enhancement (to indicate myocardial fibrosis),[29] apical hypertrophy,[29] and right ventricular wall-motion abnormalities,[30] on exercise testing, the 48-hour Holter monitor, and the cardiac magnetic resonance scan, respectively. There was 100% concurrence between echocardiography and cardiac magnetic resonance for maximal LVWT measurements in all black athletes with LVH.

Discussion

Recent studies indicate that black male athletes exhibit a higher prevalence of LVH and repolarization changes than white male athletes.[10,11,31,32] The present study is the first to specifically examine the adaptive changes in response to exercise in female international African/Afro-Caribbean athletes and is of particular clinical relevance because black female athletes form an increasing population of high-profile international competitors in the Western world. Compared with the largest published study in white female athletes (n=600),[8] only 240 black females were studied; however, when one considers that black female athletes currently constitute fewer than 10% of all athletes participating at the national level in the United Kingdom and France, the study cohort represents a sizeable proportion of athletes available for comparisons and inferences.

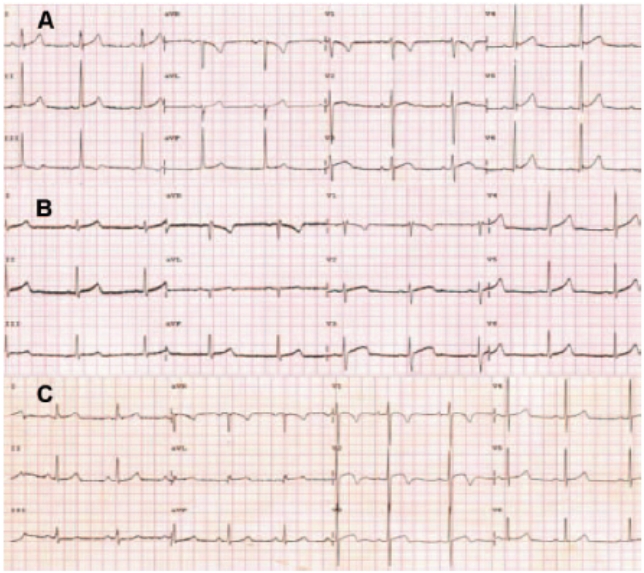

Figure 3. Spectra of ECG observations in black athletes revealing Sokolow-Lyon voltage criteria for LVH and elevated J point in the lateral leads (A), partial right bundle-branch block with accompanying convex ST-segment elevation in leads V_1 through V_3 (B), and convex ST-segment elevation and deep T-wave inversions in leads V_1 through V_3 (C).

Black Athletes With LVH

As with black male athletes,[10] highly trained female athletes of African/Afro-Caribbean descent demonstrated a greater maximal LVWT and LVM than white athletes of similar age, size, and sporting discipline. Consistent with previous reports, none of the white athletes exhibited an LVWT >11 mm.[4,5,6,9] In contrast, 8 black athletes (3%) demonstrated a maximal LVWT >11 mm (12 to 13 mm) that could have been consistent with morphologically mild HCM. None of the 8 black athletes revealed any further phenotypic features of HCM on further clinical evaluation (Table 3).[33] Importantly, because none of the black athletes exhibited an LVWT >13 mm, it would be reasonable to infer that an absolute maximal LVWT of 13 mm probably represents the physiological upper limit of LVH in an asymptomatic black athlete outside the context of a family history of HCM, and an LVWT >13 mm may be considered to represent pathological LVH.

Black athletes with LVH participated in basketball, football, judo, netball, sprinting, and wrestling, sports that are not traditionally associated with physiological LVH in white athletes, which indicates that the isotonic and isometric stresses of sport induce more cardiac hypertrophy in black athletes than in white athletes. Direct comparisons could not be made in sporting disciplines characteristically associated with a greater LVWT in whites, such as rowing, canoeing, and cycling,[4–6] because black female athletes in the United Kingdom and France do not usually excel in such sporting disciplines. Nevertheless, none of the studies in white women participating in these sporting disciplines have reported an LVWT >11 mm.[4–6,8,9]

Differences in Repolarization Changes Between Black Athletes and White Athletes

Black female athletes exhibited a greater prevalence of T-wave inversions than white athletes. T-wave inversions were confined to V_1 through V_3 and did not appear to be determined by age, body size, sporting discipline, or cardiac dimensions. In particular, athletes with T-wave inversions did not reveal any phenotypic features of HCM[33] or arrhythmogenic right ventricular cardiomyopathy[34] on subsequent evaluation.

The prevalence and magnitude of these electric changes remain significantly lower than those observed among black male athletes[10] but higher than those reported in white male athletes.[2,3] Although the relative risk of sudden cardiac death during sport in women is considerably lower than in men, female athletes are not exempt from cardiac fatalities during sport[35–37]; therefore, the observation that normal healthy black female athletes may demonstrate physiological LVH >11 mm and T-wave inversions that mimic morphologically mild HCM is a major finding and has potential implications in relation to preparticipation cardiovascular screening programs.[38] However, unlike HCM, none of the black athletes in the present study exhibited deep T-wave inversions in the inferior or lateral leads; therefore, the identification of deep T-wave inversions in these leads in a black female with LVH may be representative of pathology rather than physiology.

Potential Mechanisms for Ethnic Differences in Electric and Structural Cardiac Manifestations

The precise mechanisms for the exaggerated myocardial hypertrophy and ECG appearances in black athletes in response to exercise are yet to be elucidated. There may be racial and gender differences in response to the modulations in BP that occur during systematic training; however, our own experience of exercising male black and white athletes with LVH has not demonstrated any significant differences in exercise-related BP responses between the ethnic groups.[10]

Racial and gender differences in large-artery structure and function,[39] endothelial function,[40] the renin-angiotensin system,[41] and levels of vasoactive cytokines[42] are recognized and may partially explain the differences in the magnitude of LVH between black athletes and white athletes and the greater predilection to LVH in male athletes in both ethnic groups, respectively. Recent in vitro and animal studies indicate that physiological LVH is mediated by the effects of insulin-like growth factor 1[43] on the phosphatidylinsitol-3-kinase–Akt1[44] pathway, which appears to regulate downstream transcription factor and gene product production.[45] It is possible that potential race-related polymorphisms in the function of insulin-like growth factor 1 within the African population may also provide an explanation for the greater magnitude of LVH observed in black athletes.

It is historically recognized that a significant proportion of normal black men and women exhibit T-wave inversions in the right precordial leads extending to V_3 and V_4.[46,47] Our own experience also suggests that black athletes may acquire such T-wave inversions in the right precordial leads during physical training (Figure 2) that are not related to cardiac structure and that regress after a 6- to 8-week period of deconditioning. Alterations in autonomic cardiac innervation, either reduced sympathetic or increased vagal tone, or recently identified sodium channel polymorphisms among the black population[48] may provide some explanation for the variation found within black athletes; however, more detailed molecular assessment and longitudinal follow-up of black athletes is necessary to unravel the intriguing manifestations of the black athlete's heart.

The authors recognize that misuse of performance-enhancing substances may be associated with LVH and marked repolarization changes[49]; however, all athletes studied were part of national and international squads and as such underwent regular testing for the presence of such substances. Hence, all subjects were considered free from compounds that could have adversely affected the results of the present study.

Conclusions

Systematic physical exercise in black female athletes is associated with greater LVH and higher prevalence of repolarization changes than in white female athletes of similar age and size participating in identical sporting disciplines. However, a maximal LVWT >13 mm or deep T-wave inversions in the inferior and lateral leads are rare and warrant further investigation.

Study Limitations

The study exhibits some limitations that warrant mention. Although a substantial number of black athletes were studied, a relatively limited number of sporting disciplines were examined compared with previous studies in whites for

reasons outlined above. The study was confined to black athletes competing in the United Kingdom and France, and although we are confident that our observations are an accurate representation of black athletes in Europe, caution must be exercised when our conclusions are extrapolated to apply to black athletes in other parts of the world. Finally, the study was cross-sectional in design; therefore, it is possible that some black athletes exhibiting LVH or marked repolarization abnormalities may have had HCM but were unidentified owing to incomplete expression of the disease phenotype, which calls for longitudinal studies in black athletes with LVH and/or marked repolarization changes in the future.

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References

1. Huston TP, Puffer JC, Rodney WM. The athletic heart syndrome. *N Engl J Med*. 1985;313:24–32.
2. Sharma S, Whyte G, Elliott P, Padula M, Kaushal R, Mahon N, McKenna WJ. Electrocardiographic changes in 1000 highly trained junior elite athletes. *Br J Sports Med*. 1999;33:319–324.
3. Pelliccia A, Maron BJ, Culasson F, Di Paolo FM, Spartaro A, Biffi A, Caselli G, Piovano P. Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation*. 2000;102:278–284.
4. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med*. 1991;324:295–301.
5. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiological limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;40:1431–1436.
6. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart: a meta-analysis of cardiac structure and function. *Circulation*. 2000;101:336–344.
7. Sharma S, Elliott PM, Whyte G, Mahon N, Virdee MS, Mist B, McKenna WJ. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. *J Am Coll Cardiol*. 2000;36:864–870.
8. Pelliccia A, Maron BJ, Culasso F, Spataro A, Caselli G. Athlete's heart in women: echocardiographic characterization of highly trained elite female athletes. *JAMA*. 1996;276:211–215.
9. Whyte GP, George K, Nevil A, Shave R, Sharma S, McKenna WJ. Left ventricular morphology and function in female athletes: a meta-analysis. *Int J Sports Med*. 2004;25:380–383.
10. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, Sharma S. Ethnic differences in left ventricular remodelling in highly-trained athletes: relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2008;51:2256–2262.
11. Magalski A, Maron BJ, Main ML, McCoy M, Florez A, Reid KJ, Epps HW, Bates J, Browne JE. Relation of race to electrocardiographic patterns in elite American football players. *J Am Coll Cardiol*. 2008;51:2250–2255.
12. Corrado D, Pelliccia A, Bjørnstad HH, Vanhees L, Biffi A, Borjesson M, Panhuyzen-Goedkoop N, Deligiannis A, Solberg E, Dugmore D, Mellwig KP, Assanelli D, Delise P, van Buuren F, Anastasakis A, Heidbuchel H, Hoffmann E, Fagard R, Priori SG, Basso C, Arbustini E, Blomstrom-Lundqvist C, McKenna WJ, Thiene G. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol: consensus statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J*. 2005;26:516–520.
13. Bille K, Figuiras D, Schamasch P. Sudden cardiac death in athletes: the Lausanne recommendations. *Eur J Cardiovasc Prev Rehabil*. 2006;13:859–875.
14. Dvorak J, Junge A, Grimm K, Kirkendall D. Medical report from the 2006 FIFA world cup Germany. *Br J Sports Med*. 2007;41:578–581.
15. Friedmann HH. *Diagnostic Electrocardiography and Vectorcardiography*. New York, NY: McGraw-Hill; 1971.
16. Bazett HC. An analysis of the time relations of electrocardiograms. *Heart*. 1920:7;353–367.
17. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy obtained by unipolar precordial and limb leads. *Am Heart J*. 1949;37:161–186.
18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St. John Sutton M, Stewart W. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7:79–108.
19. Devereux RB. Detection of left ventricular hypertrophy by M-mode echocardiography: anatomic validation, standardization and comparison to other methods. *Hypertension*. 1987;9:19–26.
20. Otterstad JE, Froeland G, St. John Sutton M, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. *Eur Heart J*. 1997;18:507–513.
21. Lewis JF, Spirito P, Pellicia A, Maron BJ. Usefulness of Doppler echocardiographic assessment of diastolic filling in distinguishing "athlete's heart" from hypertrophic cardiomyopathy. *Br Heart J*. 1992;68:296–300.
22. Nagueh SF, McFalls J, Meyer D, Hill R, Zoghbi WA, Tam JW, Quiñones MA, Roberts R, Marian AJ. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with subclinical disease. *Circulation*. 2003;108:395–398.
23. Bruce RA. Exercise testing of patients with coronary heart disease: principles and normal standards for evaluation. *Ann Clin Res*. 1971;3:323–332.
24. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. *Circulation*. 1990;82:1995–2002.
25. Monseratt L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent risk marker of sudden death in young patients. *J Am Coll Cardiol*. 2003;42:873–879.
26. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90:29–34.
27. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Inter-study reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *Am Heart J*. 2004;147:218–223.
28. Klues HG, Roberts WC, Maron BJ. Morphological determinants of echocardiographic patterns of mitral valve systolic anterior motion in hypertrophic cardiomyopathy. *Circulation*. 1993;87:1570–1579.
29. Leonardi S, Raineri C, De Ferrari GM, Ghio S, Scelsi L, Pasotti M, Tagliani M, Valentini A, Dore R, Raisaro A, Arbustini E. Usefulness of cardiac magnetic resonance in assessing the risk of ventricular arrhythmias and sudden death in patients with hypertrophic cardiomyopathy. *Eur Heart J*. 2009;30:2003–2010.
30. Sen-Chowdhry S, Prasad SK, Syrris P, Wage R, Ward D, Merrifield R, Smith GC, Firmin DN, Pennell DJ, McKenna WJ. Cardiovascular magnetic resonance in arrhythmogenic right ventricular cardiomyopathy revisited: comparison with task force criteria and genotype. *J Am Coll Cardiol*. 2006;48:2132–2140.

31. Choo JK, Abernethy WB III, Hutter AM Jr. Electrocardiographic observations in professional football players. *Am J Cardiol*. 2002;90:198–200.
32. Balady GJ, Cadigan JB, Ryan TJ. Electrogram of the athlete: an analysis of 289 professional football players. *Am J Cardiol*. 1984;53:1339–1343.
33. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH III, Spirito P, Ten Cate FJ, Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42:1687–1713.
34. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy: Task Force of the Working Group on Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J*. 1994;71:215–218.
35. Maron BJ. Sudden death in young athletes. *N Engl J Med*. 2003;349:1064–1075.
36. Eckart RE, Scoville SL, Shry EA, Potter RN, Tedrow U. Causes of sudden death in young female military recruits. *Am J Cardiol*. 2006;97:1756–1758.
37. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. *Circulation*. 2009;119:1085–1092.
38. Papadakis M, Sharma S. Electrocardiographic screening in athletes: the time is now for universal screening. *Br J Sports Med*. 2009;43:663–668.
39. Kingwell B, Boutouyrie P. Genetic influences on the arterial wall. *Clin Exp Pharmacol Physiol*. 2007;34:652–657.
40. Kalinowski L, Dobrucki IT, Malinski T. Race-specific differences in endothelial function: predisposition of African Americans to vascular diseases. *Circulation*. 2004;109:2511–2517.
41. Barley J, Blackwood A, Miller M, Markandu ND, Carter ND, Jeffery S, Cappuccio FP, MacGregor GA, Sagnella GA. Angiotensin converting enzyme gene I/D polymorphism, blood pressure and the renin-angiotensin system in Caucasian and Afro-Caribbean peoples. *J Hum Hypertens*. 1996;10:31–35.
42. Nguyen QM, Srinivasan SR, Xu JH, Chen W, Berenson GS. Racial (black-white) divergence in the association between adiponectin and arterial stiffness in asymptomatic young adults: the Bogalusa heart study. *Am J Hypertens*. 2008;21:553–557.
43. Pauliks LB, Cole KE, Mergner WJ. Increased insulin-like growth factor-1 protein in human left ventricular hypertrophy. *Exp Mol Pathol*. 1999;66:53–58.
44. DeBosch B, Treskov I, Lupa TS, Weinheimer C, Kovacs A, Courtois M, Muslin AJ. Akt1 is required for physiological cardiac growth. *Circulation*. 2006:113;2097–2104.
45. Schluter KD, Goldberg Y, Taimor G, Schafer M, Piper HM. Role of phosphatidylinositol 3-kinase activation in the hypertrophic growth of adult ventricular cardiomyocytes. *Cardiovasc Res*. 1998;40:174–181.
46. Walker AR, Walker BF. The bearing of race, sex, age and nutritional state on the precordial electrocardiograms of young South African Bantu and Caucasian subjects. *Am Heart J*. 1969;77:441–459.
47. Seriki O, Smith AJ. The electrocardiogram of young Nigerians. *Am Heart J*. 1966;72:153–157.
48. Burke A, Creighton W, Mont E, Li L, Hogan S, Kutys R, Fowler D, Virmani R. Role of SCN5A Y1102 polymorphism in sudden cardiac death in blacks. *Circulation*. 2005;112:798–802.
49. Payne JR, Kotwinski PJ, Montgomery HE. Cardiac effects of anabolic steroids. *Heart*. 2004;90:473–475.

CLINICAL PERSPECTIVE

The investigators provide novel data on physiological cardiac adaptation in highly trained female black athletes. Existing data relating to ethnic differences in exercise-related cardiovascular adaptation are confined to men and indicate a racial predilection to the development of substantial left ventricular hypertrophy and marked repolarization changes in black athletes that may overlap with hypertrophic cardiomyopathy. This study of 240 normotensive, nationally ranked black female athletes and 200 nationally ranked white athletes participating in 10 different sporting disciplines reveals that black women also exhibit greater magnitude of left ventricular hypertrophy and higher prevalence of repolarization anomalies than their white counterparts. Three percent of black athletes showed a left ventricular wall thickness >11 mm (12 to 13 mm) compared with none of the white athletes, and almost 15% demonstrated repolarization changes, including deep T-wave inversions, compared with only 2% of white athletes. In contrast to most individuals with hypertrophic cardiomyopathy, none of the black athletes exhibited a left ventricular wall thickness >13 mm or deep T-wave inversions in contiguous inferior/lateral leads, which indicates that such observations in black female athletes warrant further investigation. Application of standardized criteria derived from white athletes for differentiation of physiological adaptation from hypertrophic cardiomyopathy has the potential to result in unnecessary investigation and unfair disqualification from sport in black athletes. The study is clinically relevant in facilitating the differentiation of physiological adaptation from morphologically mild hypertrophic cardiomyopathy in black female athletes exhibiting left ventricular hypertrophy, particularly in countries where black individuals represent a high proportion of athletes competing at regional and national levels.

Appendix E

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REVIEW PAPER

Left ventricular hypertrophy in athletes

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Athlete's heart;
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Participation in regular intensive exercise is associated with a modest increase in left ventricular wall thickness (LVWT) and cavity size. The magnitude of these physiological changes is predominantly determined by a variety of demographic factors which include age, gender, size, ethnicity, and sporting discipline. A small minority of male athletes participating in sporting disciplines involving intensive isotonic and isometric exercise may exhibit substantial increases in cardiac size that overlap with the phenotypic manifestation of the cardiomyopathies. The most challenging clinical dilemma incorporates the differentiation between physiological left ventricular hypertrophy (LVH) (athlete's heart) and hypertrophic cardiomyopathy (HCM), which is recognized as the commonest cause of non-traumatic exercise related sudden cardiac death in young (<35 years old) athletes. This review aims to highlight the distribution and physiological upper limits of LVWT in athletes, determinants of LVH in athletes, and echocardiographic methods of differentiating athlete's heart from HCM.

Introduction

Regular participation in intensive physical exercise is associated with central and peripheral cardiovascular adaptations that facilitate the generation of a large and sustained cardiac output and enhance the extraction of oxygen from exercising muscle for aerobic glycolysis, respectively. An increase in cardiac size is fundamental to the ability to generate a large stroke volume. Over the past three decades, the athlete's heart has been the subject of several echocardiographic studies involving many thousands of athletes.[1–5] Most studies have been cross sectional in design and focused on Caucasian athletes aged 18–35 years. These studies provide insight into the magnitude and determinants of cardiac size in athletes and are invaluable in aiding the differentiation of physiological left ventricular hypertrophy (LVH) (athlete's heart) from hypertrophic cardiomyopathy (HCM), the leading cause of exercise related sudden cardiac death in young athletes.[6]

This review will focus predominantly on LVH, defined as an increase in left ventricular wall thickness (LVWT) >12 mm, as opposed to left ventricular mass, to place it in context with day-to-day clinical application for cardiac physiologists and clinicians. The aim of the article is to highlight the distribution of LVWT measurements in athletes, provide information on the determinants and physiological upper limits LVH, and outline echocardiographic methods of differentiating physiological LVH (athlete's heart) from HCM in an athlete with increased LVWT.

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Left ventricular wall thickness measurements in athletes

Athletic training is associated with statistically significant increases in cardiac dimensions compared with sedentary individuals. A meta-analysis of almost 1000 M-mode echocardiographic studies in highly trained male athletes showed that athletes exhibited a 15–20% increase in septal and left ventricular posterior wall thickness, respectively.[1] In terms of absolute values, however, the mean LVWT in athletes was between 10 and 11 mm and fell within the normally accepted range for sedentary individuals.

Subsequent two-dimensional echocardiographic studies in large cohorts of highly trained athletes have shown that the vast majority has an LVWT ≤12 mm and would not normally be considered to have LVH. However, a small minority of athletes exhibit substantial increases in the magnitude of LVWT measurements that overlap with those observed in patients with morphologically mild HCM. In an Italian study of 947 Italian Olympian athletes, 1.7% had an LVWT exceeding 12 mm.[4] A more recent study of 3000 highly trained British athletes revealed that 1.5% of athletes exhibited an LVWT >12 mm[7] (*Figure 1*) The maximal value for LVWT in both studies was 16 mm suggesting that an athlete with a maximal LVWT >16 mm may be considered to have pathological LVH, although there have been isolated reports of LVH of up to 19 mm[8,9] in some ultra-endurance athletes.

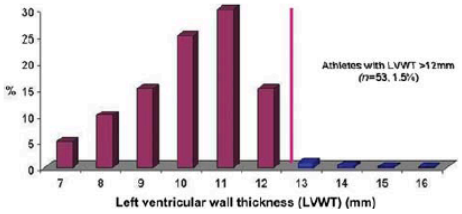

Figure 1 Distribution of left ventricular wall thickness in 3500 highly trained athletes demonstrating that ~2% athletes exhibit a left ventricular wall thickness >12 mm. Reproduced from Basavarajaiah *et al.*[7] with permission from the American College of Physicians.

Determinants of left ventricular hypertrophy in athletes

The magnitude of LVH in an athlete is largely determined by demographic factors including age, gender, ethnicity, size, and type of sporting discipline in which that athlete participates. Athletes with LVH (maximal LVWT >12 mm) are invariably males aged >16 years old. In a study of over 1000 female Italian athletes,[10] the largest LVWT recorded was 12 mm. A more recent study of over 700 adolescent British athletes participating in a variety of ball, racket, and endurance sports showed that none of the athletes aged <16 years old exhibited an LVWT >11 mm.[3] In this study only three (0.4%) athletes had an LVWT ≥12 mm and all were aged ≥16 years old (*Figure 2*). The inability of female athletes to develop very marked increases in LVWT is likely to be related to lower circulating androgen levels. Adolescent athletes aged <16 years old are relatively physically immature and lack the ability to train at similar work loads to adult athletes. Furthermore, adolescent athletes have usually been participating in intensive exercise for a shorter duration.

The sporting discipline is an important determinant of LVH in athletes. Athletes participating ultra-endurance sport with a high isotonic and isometric component such as rowing, canoeing, swimming, cycling, and ultra-endurance running exhibit the greatest increases in LVWT. In the Italian study of 947 Olympian athletes, all 15 athletes (1.7%) with LVH participated in either rowing, canoeing, or cycling.[4] The British experience of over 3000 athletes also identified LVH in athletes participating in swimming, football, rugby, and tennis.[7] Contrary to popular belief, athletes participating in pure isometric sports such as weight lifting or wrestling rarely exhibit an LVWT >12 mm.[1] Within any sporting discipline, the size of the athlete is an important determinant of measurement; a body surface area >2.0 ms^2 increases the probability of identification of LVH.[1]

There is emerging evidence that ethnicity may have an impact on LVWT measurements in athletes. An initial study of 260 black American inter-collegiate athletes showed that 13% of the athletes exhibited LVH, with LVWT measurements ranging from 13 to 18 mm.[11] A more recent study, utilizing more modern echocardiographic technology with enhanced endocardial resolution, compared LVWT measurements in 300 black male athletes competing at regional or national level with 300 white male athletes of similar calibre.[12] The two groups were of similar age and size and participated in football, rugby, tennis, boxing, sprinting,

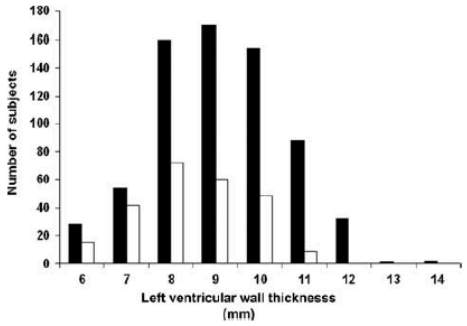

Figure 2 Distribution of left ventricular wall thickness in 720 highly trained adolescent athletes (black bars) and 250 controls (white bars). Reproduced from Sharma *et al.*[3] with permission from the American college of Physicians.

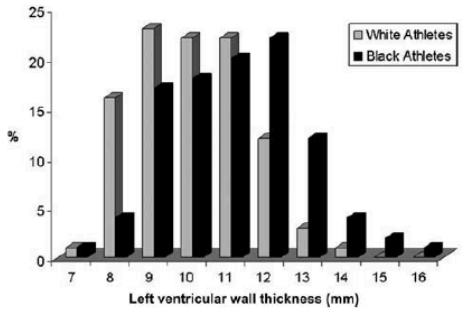

Figure 3 Distribution of left ventricular wall thickness in 300 highly trained black male athletes and 300 white male athletes of similar age, size, and sporting calibre demonstrating that a significantly higher proportion of black athletes exhibit a wall thickness >12 mm compared with white athletes (8 vs. 3%). Reproduced from Basavarajaiah *et al.*[7] with permission from the American College of Physicians.

and athletics in equal proportions. The study revealed that 18% of black athletes exhibited LVH compared with just 4% of Caucasian athletes. Furthermore 3% of black athletes had LVH >14 mm compared with none of the Caucasian athletes (*Figure 3*). However, in concurrence with large studies in Caucasian athletes, none of the black athletes exhibited LVH >16 mm. The black athletes had greater LVWT measurements compared with white athletes in every sporting discipline examined. The two groups of athletes did not differ in basal or peak exercise blood pressure measurements indicating that genetically mediated racial factors, rather than haemodynamic factors, contribute to the greater magnitude of LVH in response to the increased cardiac preload and after load associated with exercise.

Physiological left ventricular hypertrophy (athlete's heart) or hypertrophic cardiomyopathy

A small minority of highly trained athletes exhibit substantial LVH, with values between 13 and 16 mm, which overlaps

with values observed in 10–15% of patients with morphologically mild HCM.[7] Although the vast majority of individuals with HCM are unable to excel in sport due to the cardiac handicap, the disorder displays marked morphological and functional heterogeneity and some affected individuals are capable extraordinary athletic achievements.[13]

An athlete with LVH between 12 and 16 mm represents a grey zone between the extremes of physiological adaptation and mild expression of HCM. The differentiation between physiological LVH (athlete's heart) and HCM is crucial, when one considers that HCM is the commonest cause of non-traumatic sudden death in sport among young athletes.[6] An erroneous diagnosis has the potential for serious consequences. A false diagnosis of HCM mandates disqualification from most sporting disciplines to minimize the risk of sudden death[14,15] and has profound physical, social, and psychological consequences. Conversely, an incorrect diagnosis of athlete's heart may jeopardize a young life.

The differentiation between the two entities is usually straightforward but in some circumstances may be challenging for even the most able cardiologist. Systematic evaluation consisting of a detailed physical and family history, the demographics of the athlete, 12-lead ECG, and echocardiography are mandatory first-line investigations. Subsequent investigation with cardiopulmonary exercise testing, cardiac magnetic resonance imaging (MRI), assessment following detraining and screening for causal genetic mutations for HCM may be necessary in equivocal cases (*Table 1*).

Table 1 Clinical features indicative of pathological left ventricular hypertrophy in the assessment of an athlete with a left ventricular wall thickness between 13 and 16 mm

Symptoms	Unexplained syncope—particularly during exercise
	Palpitations
	Shortness of breath disproportionate to the exercise performed
	Dizziness
	Chest pain
Family history	HCM in a first-degree relative
Demographics	Age <16 years old
	Female sex
	Participation in purely isometric sport
	Small body surface area
Echocardiography	Left ventricular wall thickness >16 mm
	Asymmetrical septal hypertrophy
	Small left ventricular cavity diameter in end-diastole
	Presence of systolic anterior motion of the mitral valve leaflet and associated left ventricular outflow obstruction
	Abnormal indices of diastolic function
12-Lead ECG	Pathological Q-waves
	ST segment depression
	Left bundle branch block
	T-wave inversions in the lateral/inferior leads
Cardiopulmonary exercise testing	Peak $V_{O2\ max}$ <50mL/kg/min or <120% of predicted maximum
Cardiac MRI	Demonstration of apical hypertrophy
	Demonstration of significant myocardial fibrosis with gadolinium enhancement
Detraining	Failure of regression of left ventricular hypertrophy

History and demographics

The presence of angina, breathlessness that is disproportionate to the amount of exercise being performed, palpitations, dizziness, or syncope during exertion in an athlete with LVH are ominous symptoms and highly suggestive of pathology rather than physiology. A family history of HCM in a first-degree relative in an athlete with LVH should raise the suspicion of HCM, because the disorder is inherited as an autosomal dominant trait.[16] The demographics of an athlete are pertinent when attempting to differentiate athlete's heart from HCM. The identification of LVH in a female athlete, any adolescent athlete aged <16 years old or any athlete participating in low intensity endurance sports is highly indicative of HCM, since all studies in the past three decades have confirmed LVH in adult male athletes participating in highly intensity endurance sports.[1–5]

Echocardiography

Echocardiography is pivotal in the differentiation between physiological LVH and HCM in a highly trained athlete. Information relating to the magnitude and distribution of LVH, left ventricular cavity size, associated left ventricular outflow obstruction, and indices of diastolic function is essential to resolve the diagnostic predicament.

On the basis of the large cohort studies, the physiological upper limit for LVH in a highly trained athlete is 16 mm.[1,4,7] Therefore, LVH >16 mm should be considered pathological unless co-existing echocardiographic features or subsequent investigations indicate otherwise. Physiological LVH is homogeneous and symmetrical; athletes rarely exhibit differences of >2 mm between adjacent left ventricular myocardial segments and the ratio of the inter-ventricular wall thickness to the left ventricular posterior wall thickness in end-diastole is <1.5:1.[17] In contrast, almost any pattern of hypertrophy is possible in HCM and contiguous portions of the left ventricle vary in the magnitude of LVH. Most individuals (60%) with HCM demonstrate asymmetrical septal hypertrophy and 10% reveal hypertrophy confined to the left ventricular apex.[18]

The left ventricular cavity size is the single most important discriminator between physiological LVH and HCM. Almost all athletes with physiological LVH have concomitant enlargement of the left ventricular cavity (*Figure 4*). Typical values of left ventricular cavity size in athletes with LVH range between 55 and 65 mm,[19] although in our experience ~10% of athletes with LVH exhibit normal left ventricular cavity size.[20] HCM is characterized by disparity between the magnitude of LVH and the left ventricular cavity size; LVH occurs at the expense of left ventricular cavity size. Most individuals with HCM have a small left ventricular cavity (<45 mm). In contrast with athletes, a dilated ventricle in HCM patients is a marker of end stage disease due to progressive myocardial fibrosis and is associated with impaired systolic function and significant functional limitation.[21]

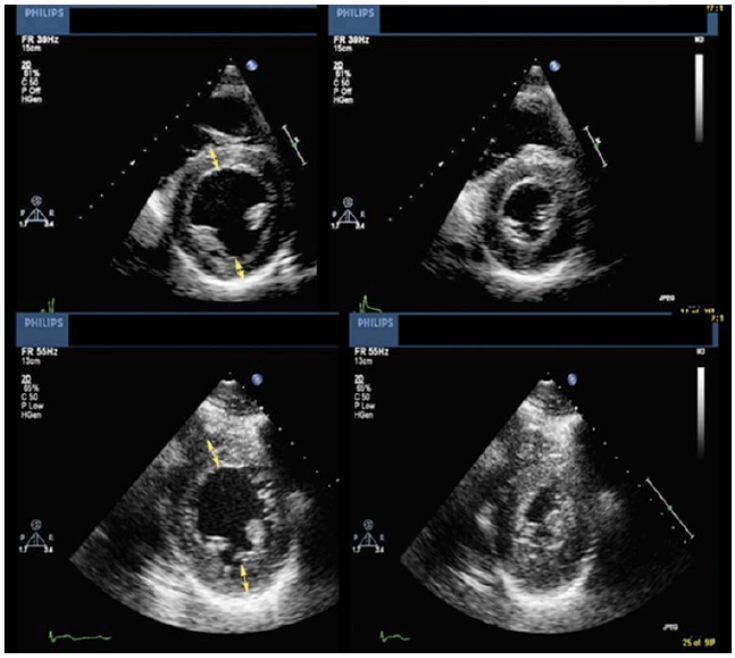

Figure 4 Mid-cavity para-sternal short axis views (diastole and systole) in an international cyclist (top) and a patient with morphologically mild hypertrophic cardiomyopathy (bottom). Showing a left ventricular wall thickness of 13 mm (arrows) in both individuals. However, note the athlete has an enlarged left ventricular cavity (60 mm) when compared with the patient with HCM (44 mm).

Approximately 25% of individuals with HCM exhibit basal, dynamic left ventricular outflow tract obstruction[21] and up to 70% develop obstruction with exercise due to systolic anterior motion of the anterior mitral valve leaflet against the inter-ventricular septum.[22] The phenomenon is attributed several factors including asymmetric septal hypertrophy, a narrow left ventricular outflow tract, anteriorly displaced papillary muscles, redundant mitral valve leaflets, and hyperdynamic systolic function. The demonstration of systolic anterior motion of mitral valve leaflets and associated left ventricular outflow obstruction at rest or immediately after exercise in an athlete with LVH is considered consistent with the diagnosis of HCM.[21]

Assessment of indices of diastolic function utilizing conventional mitral valve inflow Doppler measurements and pulmonary vein Doppler are normal in athletes who have a compliant left ventricle that is capable of filling sufficiently to maintain a high stroke volume even at almost maximal rates.[23] In contrast, individuals with HCM have LVH associated with increased muscle stiffness due to myocyte disarray and myocardial fibrosis as well as impaired sarcoplasmic calcium kinetics resulting in impaired myocardial relaxation. Consequently early (rapid), passive left ventricular filling is impaired as evidenced by the demonstration of a reversed E:A ratio, prolonged E-deceleration time (>240 ms), or isovolumic relaxation times (>90 ms), reversed S/D ratio during pulmonary vein Doppler.[24]

Recent studies utilizing colour coded and pulsed-tissue Doppler echocardiography have provided more sensitive and specific methods of differentiating physiological LVH from morphologically mild HCM.[25,26] Measurement of myocardial velocity gradients from digitized M-mode colour Doppler reveals that individuals with HCM exhibit impaired myocardial filling during the rapid filling phase of diastole and display reduced left ventricular posterior wall myocardial velocity gradients compared with athletes. Indeed, a small study comparing 25 individuals with HCM and 21 athletes with physiological LVH indicates that a myocardial velocity gradient of $<7\ s^{-1}$ measured in early diastole, may be regarded as a sensitive and specific method of differentiating individuals with HCM from athletes with physiological LVH.[27]

Assessment of longitudinal cardiac function with pulsed-tissue Doppler at the level of the mitral valve annulus has demonstrated that individuals with morphologically mild HCM, including those with normal mitral valve inflow Doppler measurements, exhibit lower early diastolic velocities (Ea or E') compared with athletes. An E' of <9 cm/s favours pathological LVH with a sensitivity approaching 90%.[28] The E/E' ratio may also be useful is differentiating physiological LVH from HCM.[29] A $E/E' >12$ is indicative of high left atrial filling pressures, a recognized pathophysiological hallmark of HCM, however most trained athletes exhibit a $E/E' <8$.

Our experience of differentiating physiological LVH from HCM suggests that although small studies comparing athletes with physiological LVH and those with morphologically mild LVH have derived numerical parameters of diastolic function

that facilitate the differentiation between the two entities, none of the aforementioned indices of diastolic function can be reliably utilized to confirm or refute the diagnosis of HCM in an athlete with LVH in every case.

Measurement of systolic function using conventional methods based on the percentage change of left ventricular volume between systole and diastole has always suggested that individuals with HCM have a high systolic ejection fraction. However, in the presence of small left ventricular cavity size, modest changes in the absolute volume of the left ventricle between systole and diastole results in a significantly higher calculated percentage change. The disorder is characterized by asymmetrical abnormalities of myocardial architecture as well as patchy myocardial fibrosis; therefore abnormal systolic function should be expected. Indeed pulsed-tissue Doppler studies have shown that many individuals with HCM exhibit impaired longitudinal systolic function. The identification of a mitral valve annular peak systolic velocity of <9 cm/s in an athlete with LVH should raise the suspicion of underlying pathology.[30]

Measurement of myocardial deformation (strain imaging), by either colour coded tissue Doppler or more recently two-dimensional speckle tracking, has improved our ability to quantify regional myocardial function. A recent study[31] demonstrated that in patients with HCM strain and strain rate are abnormal even in the absence of myocardial fibrosis on cardiac MRI. Conversely, studies in athletes with LVH reveal normal circumferential, radial, and longitudinal profiles[32,33] raising the possibility that myocardial strain imaging is yet another echocardiographic modality that may facilitate the differentiation between athlete's heart and HCM (*Figure 5*).

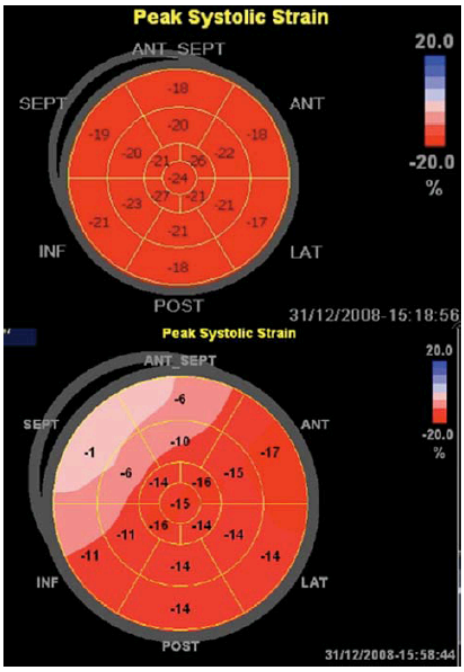

Figure 5 'Bulls eye' plots of speckle tracking derived longitudinal strain in an athlete (top) and a patient with morphologically mild hypertrophic cardiomyopathy (bottom). Paler shades represent lower peak systolic strains. Mean global strain of the athlete was -20%, compared with -14% in the HCM patient. Specifically note the reduced peak strain values in the septum/antero-septum represented by paler shades of red.

Role of 12-lead ECG, cardiopulmonary exercise stress testing, and cardiac magnetic resonance imaging

The cause of LVH in an athlete may remain equivocal despite thorough echocardiographic evaluation. Enormous advances in the molecular genetics of HCM in the past two decades raise the potential role of genetic testing to resolve the diagnostic dilemma. Unfortunately, the condition exhibits marked genetic heterogeneity with over 200 mutations in 12 different genetic loci and is time consuming, labour-intensive, and expensive.[16] The results of genetic testing are not available to the athlete in a timely fashion and the diagnostic yield is only 60–70%, therefore a negative gene test does not exclude HCM.[34] In the current era, differentiation between physiological LVH and HCM continues to rely on non-invasive clinical investigations aimed at identifying the broader phenotype of HCM. Information obtained from a 12-lead ECG, cardiopulmonary exercise testing, and cardiac MRI provides invaluable adjunctive information (*Table 1*). With respect to the 12-lead ECG, although both physiological LVH and HCM are associated with large QRS complexes in left ventricular leads, the additional presence of ST segment depression, deep (more than -0.2 mV) T-wave inversions in the lateral or inferior leads, pathological Q-waves, and left bundle branch block are highly indicative of HCM.[35,36] The identification of deep T-wave inversions in the anterior and/or lateral leads is a recognized feature of apical HCM[37] and should prompt detailed assessment of the left ventricular apex at echocardiography, employing the use of a contrast agent to define the endocardial borders if necessary.[38] In this regard, additional imaging with cardiac magnetic resonance will provide better definition of the left ventricular apex and also prove useful in the demonstration of LVH affecting the antero-lateral free wall (which may not be visualized clearly at echocardiography).[39] Gadolinium enhanced magnetic resonance may identify myocardial fibrosis in the left ventricle in some affected individuals with HCM.[31]

The measurement of peak oxygen consumption during an exercise test is a useful method of differentiating physiological LVH from HCM. Athletes, participating in endurance sports have large peak oxygen consumption. A peak oxygen consumption of >50 mL/kg/min (or $>120\%$ of that predicted for age) in an athlete with mild LVH favours physiological adaptation.[40] In contrast, most individuals with HCM have a sub-normal peak oxygen consumption irrespective of the magnitude of LVH and functional capacity, since the combination of impaired myocardial relaxation associated with a small left ventricular cavity, exercise related myocardial ischaemia, and dynamic left ventricular outflow obstruction is not conducive to the generation of

large and sustained increase in stroke volume (and therefore cardiac output).

By virtue of the diversity of the morphological and functional manifestations of HCM, there is no single investigation that will identify all athletes with HCM and diagnostic uncertainty may persist despite a plethora of cardiac investigations. In these circumstances, it is our practice to attempt to persuade the athlete to detrain for 3 months followed by echocardiographic reassessment to ensure an accurate diagnosis, on the understanding that physiological LVH should regress completely back to normal, whereas pathological LVH will persist,[41,42] albeit to a lesser extent. The detraining process is understandably associated with anxiety, and costs fitness and future team selection; however, it could be argued that it is a relatively small price to pay given the risks involved with on-going participation in strenuous exercise in an individual with HCM.

Conclusion

Most athletes exhibit modest increases in LVWT that fall within the normally accepted range for the general population. However, a small proportion of large adult male athletes usually participating in sports with a high isotonic and isometric component develop substantial LVH in the range between 13 and 16 mm which overlaps with measurements observed in morphologically mild HCM. The differentiation between physiological LVH and HCM is essential but can prove clinically challenging. Echocardiography permits detailed assessment of left ventricular structure and function and is fundamental to resolving the diagnostic dilemma. Additional investigations aimed at identifying the broad phenotype of HCM may be necessary to facilitate the differentiation between physiological LVH (athlete's heart) and HCM.

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References

1. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart: a meta-analysis of cardiac structure and function. *Circulation* 2000;**101**:336–44.
2. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991;**324**:295–301.
3. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**40**:1431–6.
4. Spirito P, Pelliccia A, Proschan MA, Granata M, Spataro A, Bellone P *et al*. Morphology of the 'athlete's heart' assessed by echocardiography in 947 elite athletes representing 27 sports. *Am J Cardiol* 1994;**74**:802–6.
5. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. *Ann Intern Med* 1975;**82**:521–4.
6. Maron BJ. Sudden death in young athletes. *N Engl J Med* 2003;**349**:1064–75.
7. Basavarajaiah S, Wilson M, Whyte G, Shah A, McKenna W, Sharma S. Prevalence of hypertrophic cardiomyopathy in highly trained athletes: relevance to pre-participation screening. *J Am Coll Cardiol* 2008;**51**:1033–9.
8. Nagashima J, Musha H, Takada H, Murayama M. New upper limit of physiologic cardiac hypertrophy in Japanese participants in the 100-km ultra marathon. *J Am Coll Cardiol* 2003;**42**:1617–23.
9. Rodriguez Reguero JJICG, Lopez de la Iglesia J, Terrados N, Gonzalez V, Cortina R, Cortina A. Prevalence and upper limit of cardiac hypertrophy in professional cyclists. *Eur J App Physiol Occup Physiol* 1995;**70**:375–8.
10. Pelliccia A, Maron BJ, Culasso F, Spataro A, Caselli G. Athlete's heart in women. Echocardiographic characterization of highly trained elite female athletes. *J Am Med Assoc* 1996;**276**:211–5.
11. Lewis JF, Maron BJ, Diggs JA, Spencer JE, Mehrotra PP, Curry CL. Preparticipation echocardiographic screening for cardiovascular disease in a large, predominantly black population of collegiate athletes. *Am J Cardiol* 1989;**64**:1029–33.
12. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A *et al*. Ethnic differences in left ventricular remodelling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2008;**51**:2256–62.
13. Cameroon Star Foe Dies. Cameroon Star Marc-Vivien Foe Dies after collapsing during an international match in France. http://news.bbc.co.uk/sport1/hi/football/3024360.stm (2 November 2008).
14. Maron BJ, Zipes DP. 36th Bethesda Conference: Eligibility Recommendations for Competitive Athletes with Cardiovascular Abnormalities. *J Am Coll Cardiol* 2005;**45**:1312–75.
15. Bille K, Figueiras D, Schamasch P, Kappenberger L, Brenner JI, Meijboom FJ *et al*. Sudden cardiac death in athletes: the Lausanne recommendations. *European journal of cardiovascular prevention and rehabilitation: official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 2006;**13**:859–75.
16. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE *et al*. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;**42**:1687–713.
17. Shapiro LMMW. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a to dimensional echocardiographic study. *J Am Coll Cardiol* 1983;**2**:437–44.
18. Klues HGSA, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995;**26**:1699–708.
19. Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med* 1999;**130**:23–31.
20. Makan J, Sharma S, Firoozi S, Whyte G, Jackson PG, McKenna WJ. Physiological upper limits of ventricular cavity size in highly trained adolescent athletes. *Heart* 2005;**91**:495–9.
21. Spirito PSC, McKenna WJ, Maron BJ. Management of hypertrophic cardiomyopathy. *N Engl J Med* 1997;**336**:775–85.
22. Maron MOI, Zenovich A, Link M, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;**114**:2232–9.
23. Lewis JF, Spirito P, Pelliccia A, Maron BJ. Usefulness of Doppler echocardiographic assessment of diastolic filling in distinguishing 'athlete's heart' from hypertrophic cardiomyopathy. *British heart journal* 1992;**68**:296–300.
24. Maron BJSP, Green KJ, Wesley YE, Bonow RO, Arce J. Non-invasive assessment of diastolic function by pulsed wave Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1987;**10**:733–42.
25. Nagueh SF, Bachinski LL, Meyer D, Hill R, Zoghbi WA, Tam JW *et al*. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation* 2001;**104**:128–30.
26. Nagueh SF, McFalls J, Meyer D, Hill R, Zoghbi WA, Tam JW *et al*. Tissue Doppler imaging predicts the development of hypertrophic cardiomyopathy in subjects with sub-clinical disease. *Circulation* 2003;**108**:395–8.
27. Palka PLA, Fleming AD, Donnelly JE, Dutka D, Starkey I, Shaw T *et al*. Differences in myocardial velocity gradient measured throughout the cardiac cycle in patients with hypertrophic cardiomyopathy, athletes and patients with left ventricular hypertrophy due to hypertension. *J Am Coll Cardiol* 1997;**30**:760–8.

28. Vinereanu DFN, Sculthorpe N, Tweddel AC, Stevens M, Fraser A. Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. *Am J Cardiol* 2001;**88**:53–8.
29. Nagueh SLN, Middleton C, Spencer W, Zoghbi W, Quinones M. Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. *Circulation* 1999;**99**:254–61.
30. Ha JWAJ, Kim JM, Choi EY, Kang SM, Rim SJ, Jang Y *et al.* Abnormal longitudinal myocardial functional reserve assessed by exercise tissue Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2006;**19**:1314–9.
31. Popović ZB, Kwon DH, Mishra M, Buakhamsri A, Greenberg NL, Thamilarasan M *et al.* Association between regional ventricular function and myocardial fibrosis in hypertrophic cardiomyopathy assessed by speckle tracking echocardiography and delayed hyper-enhancement magnetic resonance imaging. *J Am Soc Echocardiogr* 2008;**21**:1299–305.
32. Poulsen SH, Hjortshøj S, Korup E, Poenitz V, Espersen G, Søgaard P *et al.* Strain rate and tissue tracking imaging in quantification of left ventricular systolic function in endurance and strength athletes. *Scand J Med Sci Sports* 2007;**17**:148–55.
33. Richand V, Lafitte S, Reant P, Serri K, Lafitte M, Brette S *et al.* An ultrasound speckle tracking (two-dimensional strain) analysis of myocardial deformation in professional soccer players compared with healthy subjects and hypertrophic cardiomyopathy. *Am J Cardiol* 2007;**100**:128–32.
34. Maron B. Hypertrophic cardiomyopathy: a systematic review. *J Am Med Assoc* 2002;**287**:1308–20.
35. Ryan MCJ, Fench J, Joshi J, Choudhury L, Chojnowska L, Michalak E *et al.* The standard electrocardiogram as a screening test for hypertrophic cardiomyopathy. *Am J Cardiol* 1995;**76**:689–94.
36. Savage DD, Seides SF, Clark CE *et al.* Electrocardiographic findings in patients with obstructive and non-obstructive hypertrophic cardiomyopathy. *Circulation* 1978;**58**:402–8.
37. Montgomery JV, Harris KM, Casey SA, Zenovich AG, Maron BJ. Relation of electrocardiographic patterns to phenotypic expression and clinical outcome in hypertrophic cardiomyopathy. *Am J Cardiol* 2005;**96**:270–5.
38. Thanigaraj SPJ. Apical hypertrophic cardiomyopathy: echocardiographic diagnosis with the use of intravenous contrast image enhancement. *J Am Soc Echocardiogr* 2000;**13**:146–9.
39. Moon JCFN, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. *Heart* 2004;**90**:645–9.
40. Sharma S, Elliott PM, Whyte G, Mahon N, Virdee MS, Mist B *et al.* Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. *J Am Coll Cardiol* 2000;**36**:864–70.
41. Pelliccia A, Maron BJ, De Luca R, Di Paolo FM, Spataro A, Culasso F. Remodelling of left ventricular hypertrophy in elite athletes after long-term de-conditioning. *Circulation* 2002;**105**:944–9.
42. Basavarajaiah SWM, Junagde S, Jackson G, Whyte G, Sharma S, Roberts WO. Physiological left ventricular hypertrophy or hypertrophic cardiomyopathy in an elite adolescent athlete: role of detraining in resolving the clinical dilemma. *Br J Sports Med* 2006;**40**:727–9.

Appendix F

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CLINICAL RESEARCH

The prevalence, distribution, and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin

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Aims Athletic training in male black athletes (BAs) is associated with marked ECG repolarization changes that overlap with hypertrophic cardiomyopathy (HCM). Differentiating between the two entities is prudent since BAs exhibit a higher prevalence of exercise-related sudden death from HCM compared with white athletes (WAs).

Methods and results Between 1996 and 2010, 904 BAs underwent serial cardiac evaluations including ECG and echocardiography. Athletes exhibiting T-wave inversions were investigated further for HCM. Results were compared with 1819 WAs, 119 black controls (BCs), and 52 black HCM patients. Athletes were followed up for 69.7 ± 29.6 months. T-wave inversions were present in 82.7% HCM patients, 22.8% BAs, 10.1% BCs, and 3.7% WAs. In athletes, the major determinant of T-wave inversions was black ethnicity. T-wave inversions in BAs (12.7%) were predominantly confined to contiguous anterior leads (V1–V4). Only 4.1% of BAs exhibited T-wave inversions in the lateral leads. In contrast, both BCs and HCM patients exhibited lower prevalence of T-wave inversions in leads V1–V4 (4.2 and 3.8%, respectively) with most T-wave inversions in HCM patients (76.9%) involving the lateral leads. During follow-up one BA survived cardiac arrest and two athletes (one BA, one WA) were diagnosed with HCM. All three exhibited T-wave inversions in the lateral leads.

Conclusions T-wave inversions in leads V1–V4 appear to represent an ethnic variant of 'athlete's heart'. Conversely, T-wave inversions in the lateral leads may represent the initial expression of underlying cardiomyopathy and merit further evaluation and regular surveillance.

Keywords Athlete's heart • Echocardiography • Electrocardiography • Ethnicity • Hypertrophic cardiomyopathy

Introduction

Participation in regular, intensive exercise is associated with repolarization changes affecting the ST-segment and T-wave morphology.[1,2] Certain electrical anomalies occasionally overlap with those observed in cardiomyopathies.[3,4] Data from Caucasian athletes [white athletes (WAs)] suggest that 3–4% of athletes exhibit T-wave inversions but their precise significance remains controversial.[1,2,5] Whereas, some authorities regard T-wave inversions to represent physiological variants, a recent longitudinal study reported sudden cardiac deaths (SCDs) from cardiomyopathy in a small proportion of athletes harbouring such repolarization changes.[6]

Limited studies in American football players reveal that athletes of African/Afro-Caribbean origin [black athletes (BAs)] exhibit a greater prevalence of T-wave inversions than WAs.[7,8] In the

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absence of detailed investigation and longitudinal follow-up, it is uncertain whether T-wave inversions in BAs represent benign ethnic variants of physiological cardiovascular adaptation or potential harbingers of life-threatening cardiac disease. The issue is complicated further because BAs frequently exhibit left ventricular hypertrophy (LVH) which, in the context of co-existent repolarization anomalies, poses significant challenges in differentiating physiological LVH from hypertrophic cardiomyopathy (HCM).[9] This conundrum is of particular significance since exercise-related SCD secondary to HCM in the USA is reportedly higher in BAs.[10] Moreover, a growing number of scientific and sporting bodies recommend/mandate preparticipation cardiac evaluation utilizing 12-lead ECG criteria denoting abnormal results, solely derived from WAs.[11,12] Extrapolation of such criteria to BAs raises the possibility of unnecessary investigation and anxiety, false diagnoses, and potential disqualification from sport.

This study aimed to identify the prevalence and significance of T-wave inversions in highly trained male BAs to facilitate the differentiation between 'black athlete's heart' and HCM.

Methods

Setting

The SCD of several athletes has led many sporting organizations to implement preparticipation evaluation to aid the identification of athletes at risk. Neither the UK nor France offers state-funded cardiovascular preparticipation evaluation. In the UK, the charitable organization Cardiac Risk in the Young subsidizes cardiovascular evaluations for several elite sporting organizations that self-fund evaluations for recruits competing at regional, national, or international level. In France, athletes competing at national or international level are legally obliged to undergo cardiovascular evaluation comprising annual ECG and at least one echocardiogram in their career.

Athletes

Between 1996 and 2010, 2745 male athletes aged 14–35 years were evaluated in the UK and France. Athletes competed at regional, national, or international level. All athletes underwent at least one preparticipation evaluation comprising of a health questionnaire relating to training activity, presence of cardiac symptoms, family history of cardiomyopathy or premature ($\leq$40 years) SCD and drug history, cardiovascular examination, 12-lead ECG, and 2D echocardiography. Black ethnicity was determined through self-reported questionnaires.

Twenty-two athletes were excluded based on blood pressure readings >140 mmHg systolic and/or >90 mmHg diastolic. The final cohort comprised of 904 BAs and 1819 WAs.

Black controls

The charitable organization Cardiac Risk in the Young also offers cardiovascular evaluation for conditions predisposing to SCD to all young individuals who wish to be tested irrespective of their athletic status. Evaluations are performed throughout the UK and comprise of a health questionnaire, cardiovascular examination, and 12-lead ECG, identical to that performed in athletes. As part of recruitment of healthy black controls (BCs) for this study, we offered all black individuals attending for evaluation an on site 2D echocardiogram.

Between 2006 and 2010, a total of 7326 individuals were assessed. Selection criteria for inclusion as a control in our study included: black ethnicity, male sex, age 14–35 years, sedentary life style defined as $\leq$2 h of organized physical activity per week, absence of cardiac symptoms, drug history and family history of cardiomyopathy, or premature ($\leq$40 years) SCD as well as a structurally normal heart. The final cohort comprised of 119 consecutive, black, sedentary individuals.

Hypertrophic cardiomyopathy patients

Between 2001 and 2010, 155 consecutive patients with HCM were assessed in three specialist cardiomyopathy clinics in South London. These clinics serve populations consisting of a high proportion of individuals of African/Afro-Caribbean descent, reaching as high as 30% in some areas, compared with the average UK national black population of only 2%. Most patients with HCM were diagnosed either following primary care referrals for symptoms, identification of a cardiac murmur or an abnormal ECG or during cardiovascular evaluation in the context of a family history of HCM or SCD, whereas others were referred from district hospitals for specialist opinion.

Hypertrophic cardiomyopathy was defined as LVH with a maximal end-diastolic left ventricular wall thickness (max-LVWT) $\geq$15 mm in the absence of a cardiac or systemic cause, or a max-LVWT <15 mm in the context of electrocardiographic repolarization anomalies and identification of HCM in a first-degree relative. Only patients of African/Afro-Caribbean (black) ethnicity were included. Patients subject to therapeutic interventions potentially affecting repolarization patterns, such as septal myomectomy or pacemaker dependent patients, were excluded. A total of 52 patients with HCM fulfilled all inclusion criteria.

Electrocardiography

Standard 12-lead ECGs were performed using a GE Marquette Hellige (Milwaukee, WI, USA) or Philips Pagewriter Trim III (Bothel, WA, USA), as described elsewhere.[13] ST-segment shift and T-wave inversions were considered to represent repolarization abnormalities. ST-segment shift was considered significant if $\geq$0.1 mV in $\geq$2 contiguous leads. T-wave inversion of ≥ -0.1 mV in $\geq$2 leads was considered significant, (excluding AVR, V1 + lead III in isolation). Biphasic T-wave inversion was counted as abnormal if the negative deflection of the T-wave exceeded ≥ -0.1 mV. The distribution of T-wave inversions was classified into three groups: (i) T-wave inversions confined to the anterior leads (V1–V4), (ii) T-wave inversions involving the inferior leads (II, III, AVF), and (iii) T-wave inversions involving the lateral leads (I, AVL, V5, V6). Deep T-wave inversions were defined as a T-wave deflection ≥ -0.2 mV. Left ventricular hypertrophy was identified using the Sokolow–Lyon criterion.[14] Left atrial enlargement was defined as a bi-phasic P-wave in lead V1 where the negative portion was $\geq$0.1 mV deep and $\geq$0.04 s in duration, while Q-waves were considered pathological if $\geq$0.04 s in duration or $\geq$25% of the height of the ensuing R-wave. Left QRS-axis deviation was defined as a frontal axis of -30° to -90°.

All ECGs were read independently by the two senior authors (S.S. and F.C.) in the UK and France, respectively, who are highly experienced in sports cardiology and HCM.

Echocardiography

Two-dimensional echocardiography was performed using either an Accuson Computed Sono-graph 128XP/10c (San Jose, CA, USA), GE Vivid I (Tirat, Israel), Philips Sonos 7500, Philips iE33 or Philips CPX50 (Bothel, WA, USA). Standard views were obtained and cavity and wall thickness measurements were performed using established guidelines.[15] Left atrial diameter and left ventricular internal diameter were measured from the parasternal long-axis view using the two-dimensional images. Left ventricular wall thickness was

measured in the two-dimensional parasternal short-axis view, at the levels of the mitral valve and papillary muscles; the greatest measurement was defined as the max-LVWT. Left ventricular mass (LVM) was calculated with the formula of Devereux.[16] Two-dimensional continuous- and pulsed-Doppler imaging were performed using standard parasternal and apical views.[17] The systolic pulmonary artery pressure was estimated using the simplified Bernoulli equation ($4V^2_{max}$ + right atrial pressure), where V_{max} is the maximal velocity of the tricuspid regurgitant jet measured using continuous-wave Doppler in the four-chamber view.[18] In the absence of a raised jugular venous pressure during cardiovascular examination in any of the athletes, the right atrial pressure was assumed to be 5 mmHg. A cardiologist blinded to the athlete's identity reviewed all scans.

Further evaluation and follow-up

Athletes with significant T-wave inversions ± ST-segment depression and those exhibiting a max-LVWT >12 mm were invited for further clinical evaluation including upright exercise stress testing ± cardiopulmonary testing,[19–22] 24–48 h Holter,[23] cardiac magnetic resonance imaging with gadolinium injection[24,25] and evaluation of first-degree relatives, to check for the broader phenotype of underlying cardiomyopathies, in particular HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Several athletes underwent repeat cardiac evaluations in accordance with the policies of their sporting organizations irrespective of baseline results.

Ethical approval/consent

In the UK, ethical approval was granted by the National Research Ethics Service, Essex 2 Research Ethics Committee. In France, the study was approved by the French Ministry of health and youth. Written consent was obtained from individuals aged ≥16 years and from a parent/guardian for those aged <16 years.

Statistical analysis

Statistical analyses were performed using SPSS software, version 16 (Chicago, IL, USA). Variables were tested for normality using the Kolmogorov–Smirnov test. Values were expressed as mean ± standard deviation (SD) or percentages, as appropriate. Group differences were tested using Student's *t*-test or one-way ANOVA (Sidak test for *post hoc* analysis) and Mann–Whitney *U* or Kruskal–Wallis (Dunn's test for *post hoc* analyses) tests for normally and non-normally distributed variables, respectively. χ^2 test or Fisher's exact test was used as appropriate to test group differences of proportions.

Univariate analyses were performed to determine variables (ethnicity, age, body surface area, hours of training/week, systolic and diastolic blood pressure, mLVWTd, and left atrial size) associated with T-wave inversions and ST-segment elevation among athletes. Binary logistic regression analyses were used to determine the independence of the above associations. The goodness of fit was evaluated using the Hosmer–Lemeshow test. Significance was defined as a two-tailed *P*-value of <0.05 throughout.

Results

Athletes

None of the athletes reported sinister cardiac symptoms, such as angina, breathlessness disproportionate to the amount of exercise being performed, palpitations, dizziness, or syncope during exertion, causing concern to the screening physician or family history of cardiomyopathy or premature SCD and none took regular medication.

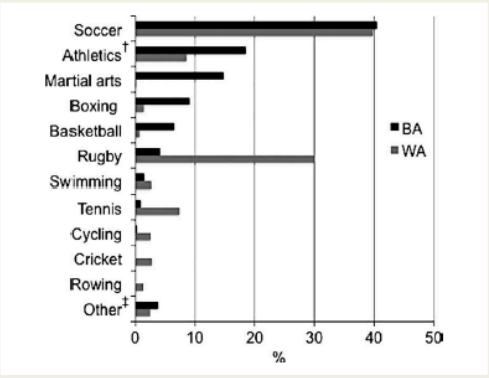

Figure 1 Sporting disciplines expressed as percentage (%) of the total black athlete (black bars) and white athlete (grey bars) cohort, respectively. †Track and field events. ‡<1% of the total cohort. White athletes: biathlon, $n = 15$; speed skating, $n = 10$; Gaelic football, $n = 7$; badminton, $n = 5$. Black athletes: weight lifting, $n = 6$; American football, $n = 5$; gymnastics, $n = 5$; fencing, $n = 5$.

Athletes competed in a total of 25 sporting disciplines (*Figure 1*). Black athletes exercised more than WAs (15.2 ± 6.1 vs. 13.1 ± 6.2 h/week, $P < 0.001$). Black athletes were older (95% aged >16 years old), had higher body surface area and higher systolic blood pressure compared with WAs (*Table 1*).

Black controls

Black sedentary individuals were younger and had lower body surface area but exhibited a higher systolic blood pressure compared with BAs (*Table 1*).

Patients with hypertrophic cardiomyopathy

Detailed demographic, clinical, echocardiographic, and electrocardiographic characteristics of black patients with HCM are reported in *Table 2*.

Prevalence and distribution of repolarization changes

Black athletes vs. white athletes

Both ST-segment elevation and T-wave inversions (including deep T-wave inversions) were commoner in BAs compared with WAs (*Table 3*). T-wave inversions in BAs were predominantly observed in the anterior leads (12.7%) (*Figure 2A* and *2B*) with only 4.1% of BAs exhibiting T-wave inversions in the lateral leads. ST-segment depression was rare in both ethnic groups.

Table 1 Comparison of demographic and echocardiographic parameters between black athletes, white athletes and black controls

Parameter	Black athletes, $n = 904$	White athletes, $n = 1819$	Black controls, $n = 119$	*P*-value
Age (years)	22.5 ± 5.0	17.4 ± 4.1	18.6 ± 6.0	<0.001[a,b,c]
BSA (m^2)	1.92 ± 0.20	1.87 ± 0.24	1.87 ± 0.24	<0.001[a,b]
Systolic BP (mmHg)	116.5 ± 13.1	111.8 ± 11.0	121.7 ± 8.4	<0.001[a,b,c]
Ao (mm)	30.2 ± 3.3	29.5 ± 3.3	28.2 ± 3.1	<0.001[a,b]
LA (mm)	35.4 ± 4.5	34.7 ± 4.7	33.0 ± 4.8	0.002[a,b]
LVED (mm)	52.6 ± 4.4	52.6 ± 4.3	47.9 ± 3.4	<0.001[b,c]
max-LVWT (mm)	10.6 ± 1.6	10.0 ± 1.2	9.2 ± 1.4	<0.001[a,b,c]
LVM (g)	203.4 ± 50.6	188.3 ± 44.1	155.2 ± 34.9	<0.001[a,b,c]
LVM/BSA (g/m^2)	103.7 ± 25.1	98.5 ± 21.8	84.0 ± 14.8	<0.001[a,b,c]
E-wave (m/s)	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	<0.001[a,b]
A-wave (m/s)	0.5 ± 0.2	0.4 ± 0.1	0.5 ± 0.1	0.34
E/A	2.1 ± 0.9	2.2 ± 0.8	2.2 ± 0.6	0.004[a]

A-wave, late diastolic mitral valve peak inflow peak velocity; Ao, aortic root; BP, blood pressure; BSA, body surface area; E-wave, early diastolic mitral valve peak inflow velocity; FS, fractional shortening; LA, left atrium; LVED, left ventricular cavity diameter in end-diastole; LVM, left ventricular mass; max-LVWT, maximal left ventricular wall thickness in end-diastole.
[a]Statistically significant between black athletes and white athletes.
[b]Statistically significant between black athletes and black controls.
[c]Statistically significant between white athletes and black controls.

Black athletes vs. black sedentary individuals vs. black patients with HCM

There were no differences in the prevalence of ST-segment elevation between BAs and BCs; however, both the athletes and controls exhibited a significantly higher prevalence of ST-segment elevation compared with individuals with HCM (63.2% BAs vs. 65.5% BCs vs. 9.6% HCM, $P < 0.001$) (*Figure 3A*). In contrast, ST segment depression was virtually absent in athletes and controls but was common in individuals with HCM (0.4% BAs vs. 0% BCs vs. 50% HCM, $P < 0.001$).

Individuals with HCM exhibited a higher prevalence of T-wave inversions (including deep T-wave inversions) compared with athletes and controls (22.8% BAs vs.10.1% BCs vs. 82.7% HCM, $P < 0.001$) (*Figure 3A*). There were also significant differences in the distribution of T-wave inversions between the groups; BAs had a higher prevalence of T-wave inversions in the anterior leads compared with BC and HCM patients (12.7% BAs vs. 4.2% BCs vs. 3.8% HCM, $P = 0.006$), whereas individuals with HCM had a higher prevalence of T-wave inversions in the lateral leads (4.1% BAs vs. 3.4% BCs vs. 76.9% HCM, $P < 0.001$). All groups revealed a similar prevalence of T-wave inversions in the inferior leads (6% BAs vs. 2.5% BCs vs. 1.9% HCM, $P = 0.21$) (*Figure 3B*).

ST-segment morphology

Several ST-segment morphologies were noted in BAs including convex ST-segments, concave/saddle-shaped and high take-off patterns (*Figure 2C*). The convex ST-segment pattern was more prevalent in BAs compared with BCs and WAs (38.4 vs. 6.7 vs. 2.7%, $P < 0.001$). Most (64.3%) T-wave inversions in the anterior leads in BAs were preceded by convex ST-segment elevation (*Figure 2B*).

Echocardiography

Both BAs and WAs exhibited greater max-LVWT and cavity size compared with BCs. Black athletes exhibited greater max-LVWT compared with WAs. In absolute terms, 112 (12.4%) BAs exhibited LVH (max-LVWT >12 mm) compared with only 29 (1.6%) WAs. The max-LVWT did not exceed 16 mm in any athlete (*Figure 4*). Athletes with LVH had normal or increased left ventricular cavity size and normal indices of diastolic function.

None of the athletes with T-wave inversions in the anterior precordial leads exhibited right ventricular hypokinesia, regional wall motion abnormalities or aneurismal bulging of the right ventricle indicative of ARVC and none had a pulmonary artery pressure of ≥30 mmHg or evidence of an intra-cardiac shunt on colour-flow echocardiography.

Exercise stress testing, Holter monitor, cardiac magnetic resonance imaging, and familial evaluation in athletes

All 350 athletes with T-wave inversions and/or LVH on echocardiography were invited to undergo further investigations to exclude the broad phenotype of HCM. Of the 350 athletes, 233 (66%) were investigated comprehensively with the full complement of tests including exercise testing, 24–48 h Holter monitor, and cardiac magnetic resonance imaging. The remaining 34% either failed to attend ($n = 62$, 18%), attended only for some of the investigations ($n = 20$, 6%), or moved clubs and could not be traced ($n = 35$, 10%).

All athletes achieved a peak-VO_2 >120% predicted. Thirteen athletes exhibited ≥100 ventricular or supra-ventricular extrasystoles over 24 h, which did not exceed >0.5% of the total heartbeats. Only one BA exhibited asymmetric septal hypertrophy

Table 2 Demographic, clinical, echocardiographic, and electrocardiographic characteristics of black patients with HCM

	Black HCM patients ($n = 52$)
Demographic and clinical characteristics (%)	
Age of diagnosis (years)	48.1 ± 17.1
Gender (males)	61.5
Family history of HCM/SCD	34.6
Patients on treatment	51.9
β-Blockers	26.9
Calcium antagonists	26.9
Amiodarone	7.7
Diuretics	17.3
Disopyramide	3.8
Intracardiac defibrillator *in situ*	5.8
Echocardiographic characteristics	
Ao (mm)	31.3 ± 3.7
LA (mm)	40.9 ± 7.3
LVED (mm)	44.0 ± 6.1
max-LVWT (mm)	17.4 ± 4.9
LVM (g)	279.6 ± 106.5
E-wave (m/s)	0.70 ± 0.18
A-wave (m/s)	0.67 ± 0.18
E/A	1.11 ± 0.44
SAM (%)	23.1
LVOT gradient ≥30 mmHg (%)	23.1
LVH pattern (%)	
ASH	25
Concentric	44.2
Apical	28.8
No hypertrophy	1.9
Electrocardiographic characteristics (%)	
LVH (Sokolow and Lyon)	53.8
LA enlargement	44.2
Pathological Q-waves	11.5
Left-axis deviation	11.5
Inverted T-waves	82.7
T-wave inversions in V1–V4	3.8
T-wave inversions in inferior leads	1.9
T-wave inversions in lateral leads	76.9
Deep T-wave inversions	69.2
ST-segment elevation	9.6
ST-segment depression	50

Where applicable results are expressed as mean ± standard deviation. A-wave, late diastolic mitral valve peak inflow peak velocity; Ao, aortic root; ASH, asymmetric septal hypertrophy, BP, blood pressure; BSA, body surface area; E-wave, early diastolic mitral valve peak inflow velocity; FS, fractional shortening; HCM, Hypertrophic cardiomyopathy; LA, left atrium; LVED, left ventricular cavity diameter in end-diastole; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVOT, left ventricular outflow tract; max-LVWT, maximal left ventricular wall thickness in end-diastole; NYHA, New York Heart Association; SAM, systolic anterior motion of the anterior mitral valve leaflet; SCD, sudden cardiac death.

(15 mm) on cardiac magnetic resonance imaging. None of the athletes revealed evidence of gadolinium enhancement. We had the opportunity to investigate first-degree relatives in only 33 (9.4%) athletes and identified HCM in one parent.

Determinants of repolarization changes in athletes

Univariate analyses demonstrated a significant association between ST-segment elevation and ethnicity, age, body surface area, hours of training/week, left atrial size, and max-LVWT. Multivariable analysis revealed that black ethnicity was the strongest independent predictor with BAs being four times more likely to exhibit ST-segment elevation compared with WAs (OR 3.95; 95% CI 2.73–5.75, $P < 0.001$). The only other predictor was the hours of training/week (OR 1.03, 95% CI 1.00–1.06, $P = 0.03$).

Univariate analysis demonstrated significant association between T-wave inversions and ethnicity, age, hours of training/week, systolic blood pressure, and max-LVWT. After adjustment for all variables, black ethnicity was the strongest independent predictor with BAs being almost six times more likely to exhibit T-wave inversions compared to WAs (OR 5.56; 95% CI 3.55–8.70, $P < 0.001$). The only other predictor identified was max-LVWT (OR 1.18; 95% CI 1.02–1.35, $P = 0.02$).

Clinical significance of repolarization changes

Of all 2723 athletes, follow-up data were available in 1243 (46%) athletes who underwent ≥2 cardiac evaluations either as part of the standard preparticipation evaluation programme or on-going clinical surveillance based on the presence of marked repolarization changes and/or LVH. During a mean follow-up of 69.7 ± 29.6 months, three athletes were diagnosed with HCM.

Athlete 1 (black soccer player) was diagnosed following an abnormal ECG showing deep T-wave inversions and ST-segment depression in the inferior and lateral leads in the context of asymmetric septal hypertrophy and a non-dilated LV cavity on echocardiography and cardiac magnetic resonance imaging (*Figure 5*). Athlete 2 (black soccer player) exhibited T-wave inversions in the inferior and lateral leads with mild concentric LVH on echocardiography and cardiac magnetic resonance imaging (*Figure 5*). These features were initially considered to represent 'athlete's heart' based on a peak-VO_2 >120% of maximum predicted and the absence of the broad HCM phenotype. The athlete was retrospectively diagnosed with HCM after successful resuscitation from ventricular fibrillation arrest during a football match. Athlete 3 (white triathlete) also exhibited T-wave inversions in the inferior and lateral leads but had a structurally normal heart on echocardiography and cardiac magnetic resonance imaging (*Figure 5*). The athlete demonstrated high peak-VO_2 and normal Holter recording but was diagnosed with HCM following identification of the apical form of HCM in his mother and subsequent confirmation with gene testing which identified a myosin-binding protein C mutation in both individuals.

Table 3 Electrocardiographic characteristics of black and white athletes

Parameter	Black athletes, $n = 904$ (%)	White athletes, $n = 1819$ (%)	Black controls, $n = 119$ (%)	*P*-value BAs vs. WAs	*P*-value BAs vs. BCs
Sinus bradycardia[a]	47.1	60.7	20.2	<0.001	<0.001
First-degree AV block	11.2	3.6	2.5	<0.001	0.003
QRS duration (ms)	88 ± 13	96 ± 10	89 ± 9	<0.001	0.42
QTc (ms)	393 ± 26	404 ± 20	400 ± 18	<0.001	0.005
Partial RBBB	24.7	12.3	5.0	<0.001	<0.001
RBBB	0.3	1.2	0	0.03	0.53
Left-axis deviation	1.1	0.6	2.5	0.10	0.20
Right-axis deviation	0.1	0.9	0	0.01	0.72
Pathological Q-waves	0.9	0.4	0	0.152	0.31
LA enlargement	8.6	2.8	5.9	<0.001	0.17
RA enlargement	6.3	0.3	2.5	<0.001	0.066
LVH	23.2	36.8	39.5	<0.001	<0.001
RVH	13.3	2.6	4.2	<0.001	<0.001
Inverted T-waves	22.8	3.7	10.1	<0.001	0.003
T-wave inversions in V1–V4	12.7	1.9	4.2	<0.001	0.007
T-wave inversions in inferior leads	6	1.5	2.5	<0.001	0.12
T-wave inversions in lateral leads	4.1	0.3	3.4	<0.001	0.70
Deep T-wave inversions	12.1	1	1.7	<0.001	0.002
ST-segment elevation	63.2	26.5	65.5	<0.001	0.61
ST-segment depression	0.4	0	0	0.01	0.47

Where applicable results are expressed as mean ± standard deviation. AV, atrioventricular; LA, left atrium; LVH, left ventricular hypertrophy; RA, right atrium; RBBB, right bundle branch block; RVH, right ventricular hypertrophy.
[a]Heart rate <60 b.p.m.

Other significant findings in athletes

Nineteen athletes (0.7%) exhibited structural or electrical abnormalities, excluding HCM: Wolff–Parkinson–White ($n = 4$), long-QT syndrome ($n = 3$), Brugada syndrome ($n = 1$), bicuspid aortic valve ($n = 3$), patent foramen ovale ($n = 3$), atrial septal defect ($n = 2$), ventricular septal defect ($n = 1$), mitral valve prolapse ($n = 1$), and cor-triatriatrum ($n = 1$).

Discussion

Cross-sectional studies in black US football players have revealed a high prevalence of repolarization changes that occasionally overlap with the phenotype observed in HCM.[7,8] This study attempted to elucidate the significance of repolarization changes in 904 BAs competing in 25 different sporting disciplines by comparing repolarization changes in BAs, with those observed in sedentary black individuals and black individuals with HCM, to facilitate differentiation between expressions of ethnicity alone, ethnic variation in physiological adaptation to exercise, and quiescent cardiac pathology. In contrast with other studies, this is the first study where all BAs were assessed with 2D echocardiography and a significant proportion of BAs, with a range of repolarization phenotypes, underwent more comprehensive evaluation and follow-up, in an attempt to provide a clinical perspective for ECG repolarization changes in BAs.

Black athletes demonstrated a high prevalence of repolarization changes; almost 25% exhibited T-wave inversions and two-thirds showed ST-segment elevation.

Ethnic differences in repolarization changes in elite athletes

Anterior leads

Black athletes exhibited a greater prevalence of T-wave inversions confined to the anterior leads compared with BCs, indicating that anterior T-wave inversions probably represent an ethnic response to physiological adaptation to exercise rather than an effect of ethnicity alone. In contrast, T-wave inversions confined to the anterior leads were uncommon in HCM. Further support that anterior T-wave inversions represent physiological adaptation comes from previously reported observations by our group demonstrating regression of anterior T-wave inversions in BAs as early as 6 weeks after cessation of exercise.[26] Although, T-wave inversions in the anterior leads are also the hallmark of ARVC,[27] our athletes with T-wave inversions did not fulfil any other criteria for ARVC during subsequent investigation. The high prevalence of T-wave inversions in the anterior leads in BAs, the co-existence of preceding ST-segment elevation in a large proportion, and the

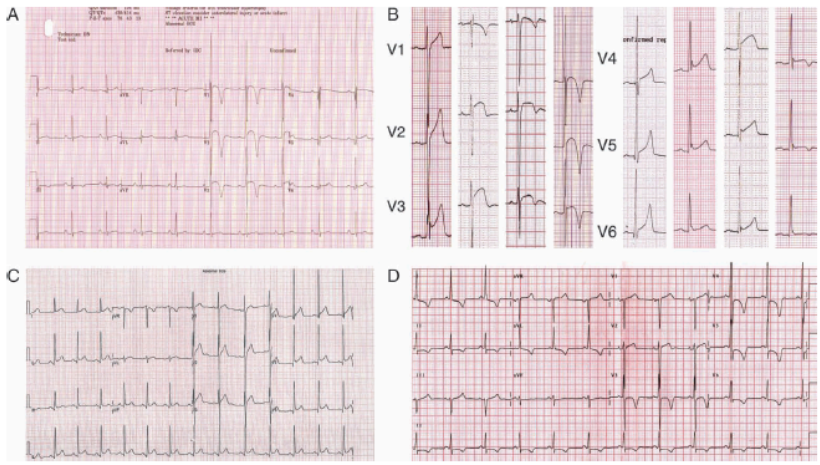

Figure 2 ECG examples demonstrating common repolarization changes in black individuals. (*A*) black long-distance runner with convex ST-segment elevation and deep T-wave inversions in leads V1–V3, (*B*) examples of common ST-segment morphologies in leads V1–V3 and V4–V6 in black athletes, (*C*) black sedentary individual with widespread ST-segment elevation of the concave/saddle-shaped and high take-off pattern, (*D*) black hypertrophic cardiomyopathy patient with ST-segment depression and deep T-wave inversions in the lateral leads.

demonstration of regression with detraining suggests that such repolarization changes are unlikely to represent ARVC.

Inferior leads

The prevalence of T-wave inversions in the inferior leads was similar in all groups. Isolated inferior T-wave inversions in the athletic groups commonly involved leads III and AVF, which in the authors' experience of 14 years of preparticipation evaluation, do not represent a malignant phenotype.

Lateral leads

T-wave inversions in the lateral leads were present in a similar proportion of black individuals irrespective of athletic activity (3–4%), implying that such ECG patterns may reflect ethnic variation in most BAs. However, the majority of patients with HCM and all 3 athletes diagnosed with the disorder during follow-up exhibited T-wave inversions in the lateral leads (*Figure 2D*), indicating that such ECG repolarization patterns should be viewed with caution in any athlete, since a proportion may represent HCM.

Our conclusion relating to the potentially sinister nature of lateral T-wave inversions is further supported by the study of Pelliccia *et al.*[6] where all athletes with marked repolarization abnormalities who were diagnosed with a cardiomyopathy during subsequent follow-up exhibited T-wave inversions in the lateral leads.

ST-segment shift

ST-segment elevation was highly prevalent in all black individuals irrespective of athletic training suggesting an ethnicity-related effect.[28,29] More detailed inspection of the morphology of the ST-segments revealed that although the concave/saddle-shaped patterns (*Figure 2B* and *C*) simulating acute pericarditis were common in both groups, convex ST-segment elevation in leads V1–V4 (*Figure 2A* and *B*) that often mimic acute anterior myocardial infarction or the Brugada phenotype, were six-fold commoner in the athletes, indicating a physiological response to training.

Clinical implications

Based on current recommendations, the identification of marked repolarization changes on an athlete's ECG is an indication for further investigation.[11] Extrapolation of ECG criteria derived from WAs would affect a considerable proportion of the elite BAs population. If consideration is given to the presence of T-wave inversions alone, almost 25% of our BAs cohort would fall within the grey zone warranting further investigations and potentially face unfair disqualification.

Following the observations in this study, the investigators would consider anterior T-wave inversions confined to leads V1–V4, especially when associated with convex ST-segment elevation, to represent an ethnically determined, physiological response to exercise. In contrast, BAs exhibiting T-wave inversions in the lateral leads or ST-segment depression warrant comprehensive cardiovascular evaluation and continued clinical surveillance, since such anomalies may represent initial or incomplete expressions of HCM. Applications of these criteria could reduce the number of BAs with repolarization changes requiring further investigations to as low as 4% and would represent major cost savings in countries with a large proportion of elite BAs.

Limitations

The follow-up period was relatively short considering event rates in HCM are low and the authors did not have complete follow-up

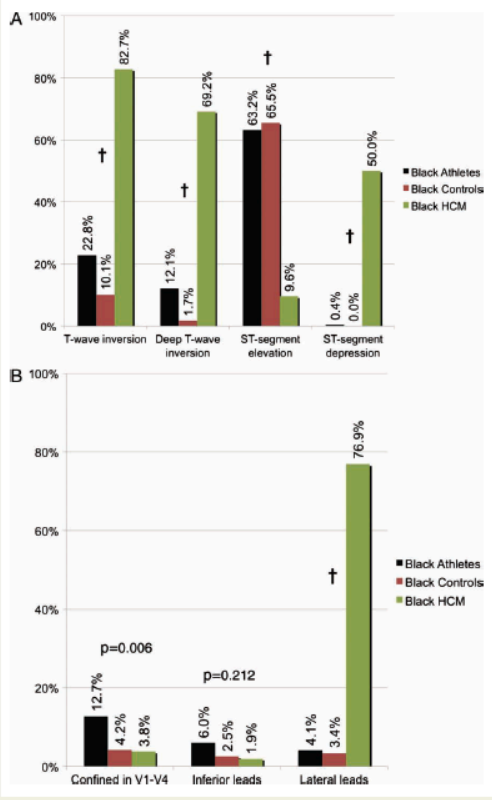

Figure 3 (*A*) Histogram demonstrating the prevalence of repolarization changes as percentage (%) of the total cohort in black athletes, black controls, and black hypertrophic cardiomyopathy patients groups. (*B*) Histogram demonstrating the distribution of T-wave inversions as percentage (%) of the total cohort in the three groups. $^{\dagger}P < 0.001$ when comparing the three groups.

data, including evaluation of first-degree relatives, in a significant number of athletes. However, follow-up data was available in a substantial number of athletes ($n = 1243$) to enable relatively accurate conclusions, especially when one takes into consideration the practical difficulties associated with motivating apparently well athletes to attend clinical institutions in the absence of perceived benefit relating to exercise performance.

The diagnosis of HCM was established only in athletes with repolarization changes and/or LVH who exhibited fatal arrhythmias, familial disease, or asymmetric septal hypertrophy with a non-dilated left ventricle. However, HCM is heterogeneous with respect to its phenotypic expression and therefore milder/more benign forms of the disorder may not have been identified. Although it is plausible that athletes without repolarization anomalies on their ECG or athletes with T-wave inversions confined in the anterior leads and those with T-wave inversions in the inferior leads may harbour quiescent disease, our follow-up findings did not provide any indicators to support this statement.

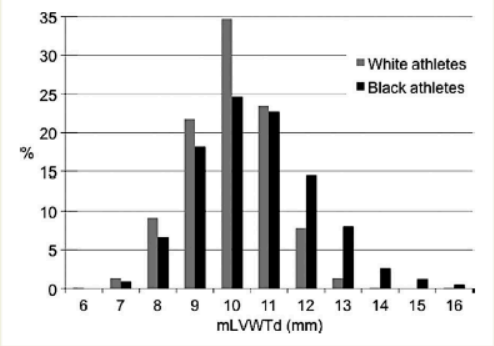

Figure 4 Histogram demonstrating the distribution of maximal left ventricular wall thickness at end-diastole (mLVWTd) as percentage (%) of the total black athlete (black bars) and white athlete (grey bars) cohort, respectively.

The authors recognize that misuse of performance-enhancing substances is associated with LVH and repolarization changes, however, most athletes studied were part of national and international squads and underwent regular testing for the presence of such substances.

Only 52 patients with HCM were included in the study, limiting the conclusions that can be deduced relating to the qualitative characteristics of black individuals with HCM. However, this number is relatively large when one considers that only 2–3% of the UK population is of African/Afro-Caribbean origin. The definition of HCM (LVH in the absence of a cardiac or systemic cause) *per se* marred a conclusive diagnosis of HCM in many affected black individuals since over 50% aged >40 years old have hypertension which is also a recognized cause of LVH.[30,31] Our predicament is supported by a multicentre American study involving 1986 HCM patients where only 8% were black.[32]

Finally, we were unable to utilize genetic testing to aid the differentiation of athlete's heart from HCM outside the context of familial disease, as per guidelines.[33]

Conclusion

The current study observed a striking association of T-wave inversions in contiguous lateral leads with a potentially fatal cardiomyopathy but event-free episodes in athletes with T-wave inversions confined to leads V1–V4, suggesting that T-wave inversions in leads V1–V4, commonly associated with convex ST-segment elevation in BAs, are likely to represent an ethnic variant of 'athlete's heart'. Conversely, T-wave inversions in the lateral leads may represent the initial expression of HCM and merit further cardiovascular evaluation and regular follow-up.

The relatively low event rate in HCM and short follow-up period of our athletes necessitates a larger, multicentre study of longer duration to validate our conclusions.

LA (mm)	IVSd (mm)	LVPWd (mm)	LVED (mm)	LVM (g)	E/A	Athlete
42	15	12	48	302	1.8	1
36	14	14	46	256	2.4	2
34	11	9	49	175	2.4	3

Figure 5 12-lead electrocardiograms and echocardiographic data of all three athletes diagnosed with hypertrophic cardiomyopathy during subsequent follow-up. Abbreviations: A, late diastolic mitral valve inflow peak velocity; E, early diastolic mitral valve peak inflow velocity; IVSd, maximal left ventricular septal wall thickness in end-diastole; LA, left atrium; LVED, left ventricular cavity diameter in end-diastole; LVM, left ventricular mass; and LVPWd, maximal left ventricular posterior wall thickness in end-diastole.

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Conflict of interest: none declared.

References

1. Papadakis M, Basavarajaiah S, Rawlins J, Edwards C, Makan J, Firoozi S, Carby L, Sharma S. Prevalence and significance of T-wave inversions in predominantly Caucasian adolescent athletes. *Eur Heart J* 2009;**20**:1728–1735.
2. Pelliccia A, Maron BJ, Culasso F, Di Paolo FM, Spartaro A, Biffi A, Caselli G, Piovano P. Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation* 2000;**102**:278–284.
3. Ryan MP, Cleland JGF, French JA, Joshi J, Choudhury L, Choinowska L, Michalak E, Al-Mahdawi S, Nihoyannopoulos P, Oakley CM. The standard electrocardiogram as a screening test for hypertrophic cardiomyopathy. *Am J Cardiol* 1995;**76**: 689–694.
4. Marcus FI. Prevalence of T-wave inversion beyond V1 in young normal individuals and usefulness for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Am J Cardiol* 2005;**95**:1070–1071.
5. Sharma S, Whyte G, Elliott P, Padula M, Kaushal R, Mahon N, McKenna WJ. Electrocardiographic changes in 1000 highly trained junior elite athletes. *Br J Sports Med* 1999;**33**:319–324.
6. Pelliccia A, Di Paolo FM, Quattrini FM, Basso C, Culasso F, Popoli G, De Luca R, Spataro A, Biffi A, Thiene G, Maron BJ. Outcomes in athletes with marked ECG repolarisation abnormalities. *N Engl J Med* 2008;**358**:152–161.
7. Choo JK, Abernethy WB III, Hutter AM Jr. Electrocardiographic observations in professional football players. *Am J Cardiol* 2002;**90**:198–200.
8. Magalski A, Maron BJ, Main ML, McCoy M, Florez A, Reid KJ, Epps HW, Bates J, Browneet JE. Relation of race to electrocardiographic patterns in elite American football players. *J Am Coll Cardiol* 2008;**51**:2250–2255.
9. Basavarajaiah S, Boraita A, Whyte G, Wilson M, Carby L, Shah A, Sharma S. Ethnic differences in left-ventricular remodeling in highly-trained athletes. Relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2008;**51**:2256–2262.
10. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes. Analysis of 1866 deaths in the United States, 1980–2006. *Circulation* 2009;**119**:1085–1092.
11. Corrado D, Pelliccia A, Bjørnstad HH, Vanhees L, Biffi A, Borjesson M, Panhuyzen-Goedkoop N, Deligiannis A, Solberg E, Dugmore D, Mellwig KP, Assanelli D, Delise P, van-Buuren F, Anastasakis A, Heidbuchel H, Hoffmann E, Fagard R, Priori SG, Basso C, Arbustini E, Blomstrom-Lundqvist C, McKenna WJ, Thiene G. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol: consensus statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J* 2005;**26**:516–520.
12. Bille K, Figuiras D, Schamasch P. Sudden cardiac death in athletes. The Lausanne recommendations. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:859–875.
13. Rawlins J, Carre F, Kervio G, Papadakis M, Chandra N, Edwards C, Whyte GP, Sharma S. Ethnic differences in physiological cardiac adaptation to intense physical exercise in highly trained female athletes. *Circulation* 2010;**121**:1078–1085.

14. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy obtained by unipolar precordial and limb leads. *Am Heart J* 1949;**37**:161–186.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, Sutton MST, Stewart W. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79–108.
16. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;**57**:450–458.
17. Lewis JF, Spirito P, Pellicia A, Maron BJ. Usefulness of Doppler echocardiographic assessment of diastolic filling in distinguishing "athlete's heart" from hypertrophic cardiomyopathy. *Br Heart J* 1992;**68**:296–300.
18. Chan KL, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of 3 Doppler ultrasound methods in the prediction of pulmonary artery pressure. *J Am Coll Cardiol* 1987;**9**:549–554.
19. Bruce RA. Exercise testing of patients with coronary artery disease. Principles and normal standards for evaluation. *Ann Clin Res* 1971;**3**:323–332.
20. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise testing in hypertrophic cardiomyopathy. *Circulation* 1990;**82**:1995–2002.
21. Sharma S, Elliott PM, Whyte G, Mahon N, Virdee MS, Mist B, McKenna WJ. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. *J Am Coll Cardiol* 2000;**36**:864–870.
22. Gimeno JR, Tome-Esteban M, Lofiego C, Hurtado J, Pantazis A, Lambiase P, Mist B, Mckenna WJ, Elliott PM. Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2009;**30**:2599–2605.
23. Monseratt L, Elliot PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent risk marker of sudden death in young patients. *J Am Coll Cardiol* 2003;**42**:873–879.
24. Grothues F, Smith GC, Moon JCC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002;**90**:29–34.
25. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function and mass with cardiovascular magnetic resonance. *Am Heart J* 2004;**147**:218–223.
26. Rawlins J, Mills P, Sharma S. ECG repolarisation abnormalities in an African descent athlete: pathologic or physiologic finding? In: Pelliccia A (ed.), *Sports Cardiology Case Book*. London, England: Springer-Verlag London Limited; 2009. p85–91.
27. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MGPJ, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Yoerger Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation* 2010;**121**:1533–1541.
28. Powel SJ. Unexplained electrocardiograms in the African. *Brit Heart J* 1959;**21**:542–548.
29. Seriki O, Smith AJ. The electrocardiogram of young Nigerians. *Am Heart J* 1966;**72**:153–157.
30. Cappuccio FP, Cook DG, Atkinson RW, Strazzullo P. Prevalence, detection, and management of cardiovascular risk factors in different ethnic groups in south London. *Heart* 1997;**78**:555–563.
31. Agyemang C, Bhopal R. Is the blood pressure of people from African origin adults in the UK higher or lower than that in European origin white people? A review of cross-sectional data. *J Hum Hypertens* 2003;**17**:523–534.
32. Maron BJ, Carney KP, Lever HM, Lewis JF, Barac I, Casey SA, Sherrid MV. Relationship of race to sudden cardiac death in competitive athletes with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003;**41**:974–980.
33. Garratt CJ. for the Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group. Clinical indications for genetic testing in familial sudden cardiac death syndromes: an HRUK position statement. *Heart* 2008;**94**:502–507.

Appendix G

European Heart Journal
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CLINICAL RESEARCH

Prevalence and significance of T-wave inversions in predominantly Caucasian adolescent athletes

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Aims Athletic activity is associated with electrocardiographic T-wave inversions in some adults, resembling those observed in cardiomyopathy. The prevalence and significance of T-wave inversions in adolescent athletes, the group most vulnerable to exercise-related sudden death from cardiomyopathy, is unknown.

Methods and results This study evaluated 1710 adolescent athletes and 400 healthy controls. Subjects with T-wave inversions underwent intensive cardiac investigations to identify a potential cause. There was no significant difference in the overall prevalence of T-wave inversions between athletes and controls (4 vs. 3%; $P > 0.05$). T-wave inversions in leads V1–V3 were largely confined to athletes and controls aged <16 years. Only 0.1% of athletes aged ≥16 years exhibited T-wave inversions beyond V2. T-wave inversions in the inferior and/or lateral leads and deep T-wave inversions occurred infrequently in athletes (1.5 and 0.8%, respectively) and were associated with a high prevalence of left ventricular hypertrophy or congenital cardiac anomalies. Despite intensive investigations, no athlete was diagnosed with a cardiomyopathy.

Conclusions T-wave inversions in V1–V3 are relatively common in athletes <16 years and probably represent the juvenile electrocardiogram pattern. In adolescent athletes, T-wave inversions beyond V2 if ≥16 years, T-wave inversions in the inferior/lateral leads and deep T-wave inversions in any lead are unusual, warranting further investigations for underlying cardiomyopathy.

Keywords Athelete's heart • Adolescent • Electrocardiography • T-wave inversion • Pre-participation

Introduction

Regular participation in intensive physical training is associated with an increase in cardiac dimensions[1,2] and pronounced cardiac vagal tone.[3] These physiological responses that are fundamental to generating and sustaining a high cardiac output for prolonged periods collectively constitute the athlete's heart and are commonly reflected on the surface electrocardiogram (ECG) in the form of high-voltage QRS complexes, sinus bradycardia, and repolarization changes.[4,5] Certain repolarization anomalies, specifically T-wave inversions, are rare in athletes but are common manifestations in individuals with hypertrophic cardiomyopathy (HCM)[6] and arrhythmogenic right ventricular cardiomyopathy (ARVC)[7] which collectively account for over one-third of all sudden cardiac deaths (SCDs) in young athletes.[8,9]

The prevalence of T-wave inversions in adult athletes is 3–4%.[5,7,10] However, neither the prevalence nor the significance of T-wave inversions in adolescent athletes have been studied in depth. Adolescent athletes and even younger children participating in competitive sport are of particular interest since they are the most vulnerable cohort at risk of exercise-related SCD from underlying cardiomyopathies.[11,12] The interpretation of the ECG in young, asymptomatic adolescent athletes can be challenging, since they often exhibit T-wave inversions in the right precordial leads (V1–V3), similar to ARVC, which are considered to represent the normal juvenile ECG pattern and large magnitude QRS complexes resembling those observed in HCM, secondary to thin chest walls.[4]

In the pre-participation screening era, accurate differentiation between ECG patterns related to physical maturation or

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physiological ventricular remodelling secondary to exercise, from HCM to ARVC, is crucial. The aim of this study was to identify the prevalence of T-wave inversions and their relationship to structural heart disease, with view to improving the identification of young athletes at risk of sudden death during sport, as well as minimizing the number of adolescent athletes subjected to unnecessary investigations following an initial pre-participation screening ECG.

Methods

Setting

The death of several professional sports persons from structural or electrical cardiac defects has led to discussions relating to pre-participation cardiovascular evaluation of all athletes for the identification of potentially sinister cardiovascular disorders prior to selection for competition. Owing to financial constraints, the UK, as with many other countries in the developed world, does not offer a state-funded cardiovascular evaluation of athletes; however, some sporting organizations provide independent, self-funded cardiovascular evaluation for all junior recruits competing (or expected to) at regional or national level. For the past 12 years, the Centre of Sports Cardiology at the Olympic Medical Institute which is funded by the charitable organisation Cardiac Risk in the Young (CRY) has been responsible for performing cardiovascular evaluations for a variety of elite sporting organizations. In some sporting organizations such as the British lawn tennis association, premier rugby league, premier league football, the national swimming, and boxing squad, cardiac evaluation is a mandatory pre-requisite prior to on-going competition. However, in other circumstances, e.g. basketball and field and track athletics, the cardiovascular evaluation of all athletes in any given club/team is performed at the jurisdiction of the club coach or doctor. The senior author (S.S.) has been responsible for conducting and supervising all screenings since 1996.

Between April 1996 and April 2008, 1710 post-pubertal adolescent athletes and 400 healthy controls underwent a cardiac evaluation, comprising of a health questionnaire relating to training activity, presence of cardiac symptoms, family history of cardiomyopathy, or premature ($\leq$40 years old) SCD and drug history, cardiovascular examination including blood pressure measurement, 12-lead ECG, and two-dimensional transthoracic echocardiography. None of the athletes were excluded on the basis of poor echocardiographic windows or unacceptable ECG tracings. Criteria for puberty were the onset of menstruation in females, and voice changes in males.

Based on responses ascertained from the health questionnaire, none of the subjects had prior symptoms suggestive of underlying cardiac disease, family history of cardiomyopathy, or premature SCD, and none of the athletes were taking any relevant medication, including performance-enhancing drugs. All subjects were normotensive with a systolic blood pressure reading of $\leq$120 mmHg and diastolic of $\leq$80 mmHg. Athletes and controls with significant T-wave inversions were investigated further with exercise tolerance testing, 48 h Holter monitor, and cardiac magnetic resonance (CMR) imaging, in an attempt to identify the broader phenotype of HCM or ARVC. All first-degree relatives of adolescents with significant T-wave inversions were invited for cardiovascular screening to check specifically for phenotypic evidence of a familial cardiomyopathy.

Ethical approval for the study was granted by Harrow Research Ethics Committee to the charity Cardiac Risk in the Young, Centre of Sports Cardiology. Written consent for cardiac evaluation was obtained from individuals aged $\geq$16 years and from a parent or guardian for those aged <16 years.

Athletes

All athletes competed at regional or national level and represented a variety of sport disciplines, including football (soccer), $n = 445$ (26%); tennis, $n = 393$ (23%); rugby, $n = 240$ (14%); swimming, $n = 171$ (10%); rowing, $n = 72$ (4%); cycling, $n = 50$ (3%); athletics $n = 48$ (3%); hurling, $n = 45$ (3%); triathlon, $n = 42$ (2.5%); netball, $n = 41$ (2.5%); badminton, $n = 40$ (2%); basketball, $n = 38$ (2%); boxing, $n = 34$ (2%); fencing, $n = 26$ (1.5%); and speed skating, $n = 25$ (1.5%), were included in the study. Of the 1710 athletes, 1414 (83%) were males and 1645 (96%) were Caucasian. The mean age and BSA were 16 ± 1.7 years (range 14–18) and 1.78 ± 0.25 m^2 (range 1.10–2.25), respectively. The amount of training per athlete averaged 11 ± 4.5 h/week (range 8–23).

Controls

The control group was derived from a database of cardiac screening performed at various secondary education schools. The authors selected 400 consecutive subjects who were of similar age, gender, and ethnicity to the athletic population, to enable appropriate comparisons between the two groups. Subjects were selected to fulfil the following criteria: (i) sedentary life style defined as <2 h of organized physical activity per week, (ii) age between 14 and 18 years old, who were post-pubertal, (iii) of similar gender to the athletic population, 330 (83%) males, and (iv) of similar ethnicity to the athletic population; 385 (96%) Caucasians. Although BSA was not part of our selection criteria, the controls were of similar BSA to the athletic population (1.76 ± 0.22 m^2).

12-Lead electrocardiogram

A standard 12-lead ECG was performed during quiet respiration in a supine position using a Marquette Hellige recorder (Milwaukee, USA). The electrodes were placed carefully to ensure consistency, and ECGs were recorded at a paper speed of 25 mm/s. Heart rate and QRS axis were calculated. P-, Q-, R-, S-, and T-wave voltages; ST-segments; QRS duration; PR interval; and QT-interval were measured in each lead using callipers and a millimetre ruler as described elsewhere.[13] The QT-interval was corrected for the heart rate (QTc) using the Bazzet's formula.[14]

Left ventricular hypertrophy (LVH) was identified using the Sokolow–Lyon criterion.[15] T-wave inversions in two or more leads were considered significant, other than in leads V1 and III. Deep T-wave inversion was defined as a negative T-wave of -0.2 mV or more in any lead.

Echocardiography

Two-dimensional echocardiography was performed by a cardiologist or a senior cardiac physiologist, using an Accuson Computed Sonograph 128XP/10c (San Jose, CA, USA) or a GE Vivid I (Tirat, Israel), both with 3 MHz transducer. Standard views were obtained as previously described.[16] Standard chamber measurements were performed as suggested by current guidelines.[17] Two-dimensional continuous- and pulsed-Doppler, as well as colour tissue-Doppler imaging were performed using standard parasternal and apical views. Left ventricular wall thickness was measured from two-dimensional short-axis views at end-diastole and the greatest measurement within the left ventricular wall was defined as the maximal wall thickness. The systolic pulmonary artery pressure was estimated using the simplified Bernoulli equation ($4V^2_{max}$ + right atrial pressure) where

V_{max} is the maximal velocity of the tricuspid regurgitant jet measured using continuous-wave Doppler.[18] In the absence of a raised jugular venous pressure during cardiovascular examination in any of the athletes, the right atrial pressure was assumed to be 5 mmHg. All scans were reviewed by a cardiologist experienced in 'athlete's heart' and cardiomyopathy.

Criteria for consideration of the diagnosis of hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy

Echocardiographic criteria for HCM were the presence of LVH, with a left ventricular wall thickness of >12 mm (based on previous studies in adolescents),[19] in association with a relatively non-dilated left ventricular cavity (<54 mm), in end-diastole and one or more of: (i) impaired diastolic function,[20] (ii) enlarged left atrial diameter (>45 mm),[21] (iii) the presence of systolic anterior motion of the anterior mitral valve leaflet and associated left ventricular outflow tract obstruction or an intra-cavity gradient, and (iv) a family history of HCM in a first-degree relative.

Owing to the inherent limitations of two-dimensional echocardiography in the assessment of the right ventricle, we considered an echocardiogram to be consistent with phenotypic features of ARVC[22] in the presence of (i) regional wall motion abnormalities in the right ventricle, (ii) impairment of the right ventricular systolic function, or (iii) aneurysmal dilation of the right ventricular cavity.

Exercise tolerance testing, 48 h Holter monitor and cardiac magnetic resonance imaging

Athletes and controls with T-wave inversions underwent an exercise stress test, 48 h Holter monitoring, and CMR scan with gadolinium enhancement.[24,25]

All subjects exercised to volitional exhaustion using the standard Bruce protocol.[26] Signals from a 12-lead ECG were displayed continuously and recorded at 1 min intervals, looking specifically for the development of arrhythmias or ischaemic changes. Blood pressure was measured by auscultation over the brachial artery at 1 min intervals during the test and for the first 3 min after the test using a mercury sphygmomanometer. A systolic blood response of >25 mmHg from baseline to peak exercise was considered normal.[26]

Ambulatory ECG monitoring was analysed for any evidence of supra-ventricular and/or ventricular arrhythmias.[27,28] Athletes were encouraged to continue their usual daily activities, including exercise during the recordings.

Cardiac magnetic resonance imaging was performed with a Siemens Sonata 1.5 T (Erlangen, Germany) using steady-state, free precession breath-hold cines (TE/TR 1.6/3.2 ms, flip angle 60°) in long-axis planes and sequential 7 mm short-axis slices (3 mm gap) from the atrioventricular ring to the apex. Late gadolinium enhancement images were acquired 10 min after intravenous gadolinium-DTPA (Schering, 0.1 mmol/kg) in identical short-axis planes using an inversion-recovery gradient echo sequence. Inversion times were adjusted to null normal myocardium (typically 320–440 ms; pixel size 1.7 × 1.4 mm). Late gadolinium enhancement images were phase swapped to exclude artefact. Ventricular volumes and function were measured for both ventricles using standard techniques[29,30] and analysed using semi-automated software (CMR tools, Cardiovascular Imaging Solutions, London, UK). All volumes and masses were indexed for age, gender, and BSA.

Assessment of first-degree relatives

First-degree relatives of all athletes and controls exhibiting significant T-wave inversions were invited to undergo cardiovascular screening. A total of 140 relatives responded to our invitation and were subjected to a health questionnaire, relating to the presence of cardiac symptoms, past medical history, drug history and a review of the family history for cardiomyopathy or premature (≤40 years old) SCD, and cardiovascular examination including blood pressure measurement, 12-lead ECG, and two-dimensional transthoracic echocardiography, to assess the possibility of familial cardiomyopathy.

Statistical analysis

Means and standard deviations (SDs) or medians and 25th–75th percentile values, where appropriate, were calculated for continuous variables. Group differences were examined using *t*-test and Mann–Whitney *U* test for parameters with normal and non-normal distributions, respectively. Chi-square or Fisher's exact test was used to test group differences of proportions. Binary logistic analysis was used to investigate the presence of an independent association between age, gender, anthropometric parameters (height, weight, BSA), type of sport (dynamic, mixed), duration (years), and intensity (hours per week) of exercise and the presence of T-wave inversion in adolescent athletes. The goodness of fit was evaluated using the Hosmer–Lemeshow test. Significance was defined as $P < 0.05$ throughout, and *P*-values were adjusted for multiple testing, where appropriate, using the Bonferroni correction. Statistical analysis was performed using SPSS software, version 14 (SPSS Inc., Chicago, IL, USA).

Results

12-Lead electrocardiogram

Electrocardiographic characteristics of adolescent athletes and controls are reported in *Table 1*.

Prevalence and distribution of T-wave inversions

There was no significant difference in the overall prevalence of T-wave inversions between adolescent athletes and sedentary individuals (4 vs. 3%; $P = 0.46$) (*Figure 1*). Deep T-wave inversions were exceedingly rare in both groups, being present in only 14 (0.8%) of the athletes (range −0.2 to −0.6 mV) and none of the control group.

The prevalence and distribution of T-wave inversions in the anterior pre-cordial leads was similar in athletes and sedentary adolescents, being present in 2.5 and 3%, respectively ($P = 0.49$). The majority of T-wave inversions in the anterior pre-cordial leads were confined to leads V1–V2, with only 0.8% of adolescent athletes and 0.5% of controls exhibiting T-wave inversions extending beyond the lead V2 (*Figure 2*). In contrast, the prevalence of T-wave inversions in the inferior and/or lateral leads differed significantly between the two groups, with a small but substantial number of athletes 25 (1.5%), but none of the controls exhibiting T-wave inversions in the inferior and/or lateral leads ($P = 0.03$).

Table 1 Electrocardiographic characteristics of adolescent athletes and controls

	Athletes (n = 1710)	Controls (n = 400)	P-value
Sinus bradycardia (heart rate <60 b.p.m.)	1368 (80%)	80 (20%)	<0.001
Sinus arrhythmia	940 (55%)	40 (10%)	<0.001
Nodal rhythm	5 (0.3%)	0	0.61
Wandering pacemaker	3 (0.2%)	0	0.92
First-degree AV block	77 (4.5%)	2 (0.5%)	<0.001
Second-degree AV block Mobitz type 1	2 (0.1%)	0	0.49
PR interval (ms)	155 ± 22 (100–245)	138 ± 17 (100–205)	<0.001
QRS duration (ms)	93 ± 12 (54–129)	88 ± 7 (65–114)	<0.001
Incomplete RBBB	513 (30%)	36 (9%)	<0.001
Complete RBBB	9 (0.6%)	0	0.30
QRS axis (degrees)	78 ± 18 (−20 to+124)	72 ± 19 (−1 to+100)	<0.001
QTc (ms)	392 ± 27 (346–450)	375 ± 29 (314–445)	<0.001
Sokolow–Lyon voltage criterion for LVH	770 (45%)	88 (22%)	<0.001
ST-segment elevation	770 (45%)	80 (20%)	<0.001
Tall T-wave (≥1 mV)	393 (23%)	24 (6%)	<0.001
T-wave inversion	67 (4%)	12 (3%)	0.46
Deep T-wave inversion (−0.2 or more, mV)	14 (0.8)	0	0.14

Where applicable, results are expressed as mean ± standard deviation with the range in parentheses. Abbreviations: AV, atrioventricular; LVH, left ventricular hypertrophy; RBBB, right bundle branch block.

T-wave inversions in relation to age, gender, body size, type, duration, and intensity of training

T-wave inversions in the anterior precordial leads, extending beyond the lead V2, were almost confined (85%) to individuals aged <16 years; of the 819 athletes aged ≥16 years, only 2 (0.2%) male athletes exhibited T-wave inversions beyond V2 when compared with 11 of the 891 (1.2%) athletes aged <16 years (P = 0.04). None of the controls aged ≥16 years exhibited T-wave inversions in the anterior precordial leads extending beyond V2.

None of the 296 female athletes exhibited T-wave inversions in the inferior and/or lateral leads or deep T-wave inversions and only 1 (0.3%) exhibited T-wave inversions in the right pre-cordial leads extending beyond lead V2.

Based on the univariable analysis, there was no significant association between age, gender, height, weight, BSA, type of sport, duration, and intensity of training with the presence of T-wave inversions in our cohort of adolescent athletes (*Table 2*).

Significance of T-wave inversions

Echocardiography

Most athletes and all the controls with T-wave inversions in the anterior precordial leads exhibited a structurally normal heart; none exhibited echocardiographic features of ARVC. None of the athletes with T-wave inversions in the anterior precordial leads had a pulmonary artery pressure of ≥30 mmHg or evidence of an intra-cardiac shunt. Although there was no correlation between T-wave inversions and left ventricular chamber size, athletes with T-wave inversions in the inferior and/or lateral leads had a high prevalence of LVH and congenital cardiac anomalies, i.e. of the 25 athletes, 10 (40%) had LVH and 2 (8%) had a congenital cardiac abnormality (mitral valve prolapse, (n = 1) and atrial septal defect, (n = 1)).

All athletes exhibiting LVH in this study were males (n = 26; 1.5%). The maximum wall thickness recorded ranged from 13 to 15 mm. All athletes with LVH were considered to have athlete's heart rather than HCM based on an enlarged left ventricular cavity, normal indices of diastolic function, and a left atrial diameter within normal limits.

Exercise tolerance testing, 48 h Holter monitor and cardiac magnetic resonance imaging

All 67 athletes and 12 controls with T-wave inversions underwent cardiopulmonary exercise stress testing, 48 h Holter monitor, and CMR, and none exhibited phenotypic evidence of HCM or ARVC.[31] With respect to the 48 h Holter monitor, six athletes and two controls with T-wave inversions exhibited ≥100 ventricular or supraventricular extrasystoles per 24 h, which did not exceed >0.5% of the total heart beats.

Assessment of first-degree relatives

From 67 athletes and 12 controls with T-wave inversions, we evaluated 140 relatives. None of the relatives exhibited phenotypic evidence of an underlying familial cardiomyopathy.

Other significant findings in adolescents screened

A total of 11 athletes (0.6%) exhibited electrical or structural abnormalities: long-QT syndrome (n = 3), Brugada syndrome (n = 1), Wolff-Parkinson White syndrome (n = 4), bicuspid

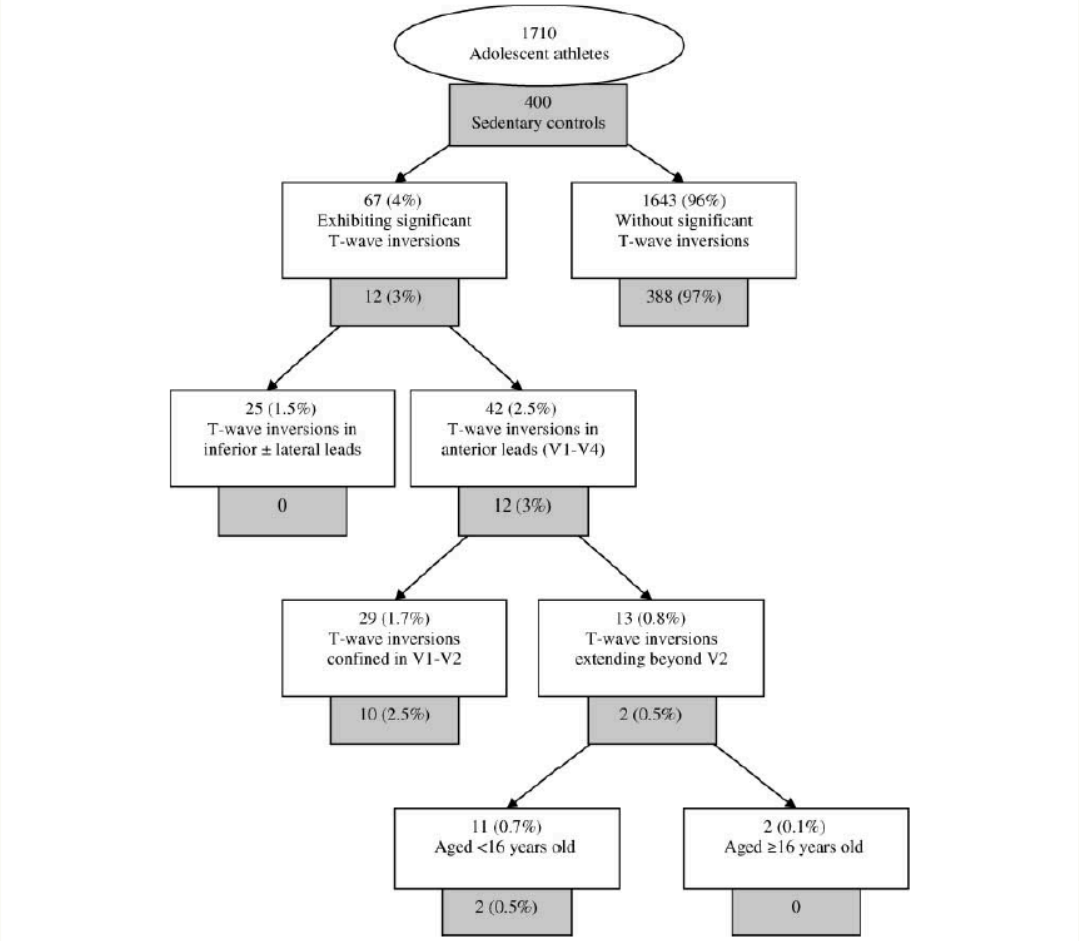

Figure 1 Diagrammatic representation of the prevalence and distribution of significant T-wave inversions in adolescent athletes (white boxes) and controls (grey boxes). Numbers in brackets express percentages (%) of each cohort.

aortic valve ($n = 2$), and cor triatriatum ($n = 1$). Only 1 (0.3%) of the 400 control subjects had an anatomical abnormality, specifically mitral valve prolapse with mild mitral regurgitation.

Discussion

T-wave inversions are regarded to be representative of the normal spectrum of cardiovascular adaptation in a minority of highly trained adult athletes. They are also, however, commonly encountered in HCM and ARVC, and it is well established that most affected individuals exhibit T-wave inversions at the time of diagnosis.[7,32,33]

Deaths from HCM and ARVC in sport are fortunately rare but are most prevalent in adolescent athletes who may exhibit T-wave inversions as part of the juvenile ECG pattern or physiological cardiac remodelling. Paradoxically, the prevalence and, more importantly, the significance of these repolarization anomalies, in this particularly vulnerable cohort of athletes, have never been evaluated in detail and magnifies the risk of a false diagnosis or conversely erroneous reassurance.

This study of over 1700 highly trained, predominantly Caucasian, athletes identified T-wave inversions in 4% of athletes, all of whom underwent intensive clinical investigations. Based on the observations of the distribution and magnitude of T-wave inversions in relation to age and gender in this study, the investigators attempt to devise a practical algorithm for selecting which asymptomatic adolescent athletes require further investigation following the initial 12-lead ECG outside the context of familial HCM or ARVC.

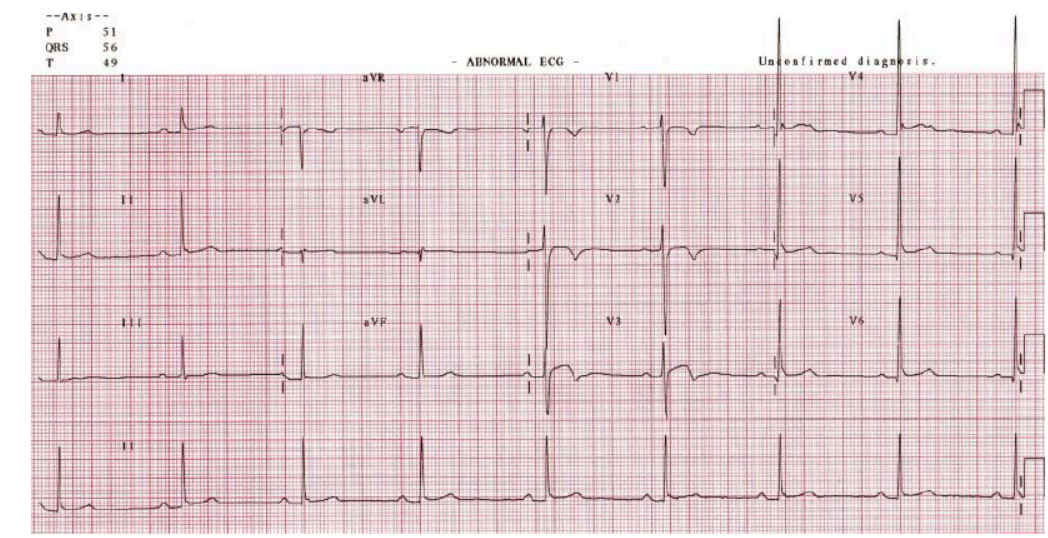

Figure 2 Electrocardiogram of a 15-year-old football player demonstrating sinus bradycardia, Sokolow–Lyon criterion for LVH and ST-segment elevation, associated with T-wave inversions in leads V1–V3. Extensive cardiac investigations, including two-dimensional echocardiogram, exercise tolerance testing, 48 h Holter monitor, cardiac magnetic resonance imaging, and family screening, did not reveal any phenotypic evidence suggestive of a diagnosis of ARVC or HCM.

Table 2 Univariate predictors of the presence of T-wave inversion in the ECG of adolescent athletes

	OR (95% CI)	*P*-value
Age (per year increment)	1.02 (0.85–1.23)	0.829
Female vs. male	0.83 (0.42–1.64)	0.591
Height (per cm increment)	0.99 (0.96–1.01)	0.341
Weight (per kg increment)	1.00 (0.99–1.02)	0.703
Body surface area (per 0.1 m^2 increment)	1.00 (0.88–1.13)	0.996
Type of sport (dynamic vs. mixed)	1.03 (0.60–1.75)	0.919
Duration of sport (per year increment)	0.98 (0.82–1.17)	0.828
Intensity of sport (per h/week increment)	1.00 (0.91–1.09)	0.949

Abbreviations: OR, odds ratio; CI, confidence interval.

Athletes with T-wave inversions in the anterior pre-cordial leads

In adolescent athletes, almost 70% of T-wave inversions in the anterior precordial leads were identified in leads V1–V2 and did not differ significantly when compared with controls. T-wave inversions extending beyond V2 were rare (0.8%) and almost confined to athletes aged <16 years old. Based on the plethora of normal investigations in both athletes and controls, we suspect that these T-wave inversions reflect the juvenile ECG pattern. On the contrary, T-wave inversions beyond V2 were identified only in two athletes aged ≥16 years. Although, the investigators were unable to identify any structural heart disease or the broader phenotype of ARVC[31] in these athletes, given the rarity of T-wave inversions in the anterior precordial leads beyond V2 in athletes aged ≥16 years, the difficulties in diagnosing ARVC in the concealed phase and the potential implications associated with the disorder, i.e. sudden death,[22,31,34] the authors cannot consider T-wave inversions beyond V2 to represent a normal variant in any athlete aged ≥16 years, without detailed investigation.

Athletes with T-wave inversions in the inferior and/or lateral leads

T-wave inversions in the inferior and/or lateral leads were present in a small (1.5%) number of athletes and were associated with a high prevalence of LVH on echocardiography or a structural abnormality of the heart. Our findings indicate that all adolescent athletes with T-wave inversions in the inferior and/or lateral leads should undergo echocardiography and further investigations, if indicated. Gender is particularly relevant to our recommendation since none of the females in our study exhibited T-wave inversions in the inferior and/or lateral leads, indicating that the presence of these repolarization anomalies are highly likely to represent a pathological myocardial substrate in young female population.

Differences between adult and adolescent athletes in relation to T-wave inversions

The prevalence of T-wave inversions in predominantly Caucasian, adolescent athletes does not appear to differ significantly from previous reports of 3–4% in adult athletes.[5,7,10] However, deep

T-wave inversions are much commoner in adult counterparts, having been documented in almost 3% of adult athletes[5] compared with just 0.8% in our study of adolescent athletes. The low prevalence of deep T-wave inversions in adolescents compared with adult athletes is probably reflective of differences in physical maturity, duration, and intensity of training between the two groups. Based on the observations of a very low frequency of deep T-wave inversions in adolescent athletes, the investigators would recommend echocardiography in all adolescent athletes exhibiting deep T-wave inversions.

Clinical applications

Cardiovascular screening in predominantly Caucasian athletes, utilizing 12-lead ECG, has been shown to be effective in reducing deaths from HCM and ARVC[35–37] and has recently been adopted by major scientific and sporting organizations.[38,39] In the current era, it is probable that junior athletes participating in competitive sport at regional, national, or international level, in many European countries will be subjected to regular cardiovascular screening. Extrapolation of data derived from adult athletes for defining an abnormal ECG could be associated with an increased number of false-positive results, unnecessary investigations, and unwarranted anxiety.

In this study the application of the ESC guidelines for an abnormal ECG derived from adult athletes would have resulted in 4% of our adolescent athletes requiring further investigations, based on the presence of significant T-wave inversions.[38] By adjusting the ECG criteria based on this large study of highly trained adolescent athletes, the number of false-positive ECGs should be reduced to a minimum, leading to a more efficient and cost-effective cardiovascular pre-participation screening in this cohort. Based on the experience of this study, the investigators favour further cardiovascular evaluation in adolescent athletes exhibiting: (i) T-wave inversions in the anterior pre-cordial leads beyond lead V2 in athletes aged $\geq$16 years, (ii) T-wave inversions in the inferior and/or lateral leads, and (iii) deep T-wave inversions in any lead. Application of these criteria would reduce the number of adolescent athletes requiring further investigation, based on the presence of T-wave inversions, in our cohort to 2%, following the initial ECG.

This study exhibits some important limitations that warrant mention. Despite intensive investigations, this study failed to identify any individual with HCM or ARVC. The investigators suspect that this was due to the relatively low number of athletes studied when one considers the prevalence of either disorder in the general population (0.2 and 0.1%, respectively), since great emphasis was placed in selecting the most elite athletic population, i.e. those competing at regional or national level. Moreover, the incidence and prevalence of both disorders, based on phenotypic manifestation, is probably considerably lower in the paediatric population when compared with adults since it is well recognized that gene carriers for HCM may not exhibit the phenotype until early adulthood and the natural history of ARVC is not fully understood.[40,41] In this regard, the investigators concede that this cross-sectional study may have failed to identify some athletes harbouring HCM or ARVC gene mutations who had not yet developed the disease phenotype, as suggested by a recent longitudinal study in Italian athletes.[42] However, the purpose of the study was to identify the prevalence and immediate significance of T-wave inversions in adolescent athletes and the investigators believe that the findings from the current study provide important clinical foundations in relation to screening of adolescent athletes. All athletes with T-wave inversions are under annual follow-up to evaluate the long-term significance of the aforementioned electrical anomalies. Finally, the investigators did not have the opportunity of evaluating the effects of ethnicity on the 12-lead ECG, and therefore the results of this study should be applied with caution to non-Caucasian athletes.

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References

1. Makan J, Sharma S, Firoozi S, Whyte G, Jackson PG, McKenna WJ. Physiological upper limits of ventricular cavity size in highly trained adolescent athletes. *Heart* 2005;**91**:495–499.
2. Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med* 1999;**130**:23–31.
3. Smith ML, Hudson DL, Graitzer HM, Raven PB. Exercise training bradycardia: the role of autonomic balance. *Med Sci Sports Exerc* 1989;**21**:40–44.
4. Sharma S, Whyte G, Elliott P *et al.* Electrocardiographic changes in 1000 highly trained junior elite athletes. *Br J Sports Med* 1999;**33**:319–324.
5. Pelliccia A, Maron BJ, Culasson F, Di Paolo FM, Spartaro A, Biffi A, Caselli G, Piovano P. Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation* 2000;**102**:278–284.
6. Ryan MP, Cleland JGF, French JA, Joshi J, Choudhury L, Choinowska L, Michalak E, Al-Mahdawi S, Nihoyannopoulos P, Oakley CM. The standard electrocardiogram as a screening test for hypertrophic cardiomyopathy. *Am J Cardiol* 1995;**76**:689–694.
7. Marcus FI. Prevalence of T-wave inversion beyond V1 in young normal individuals and usefulness for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Am J Cardiol* 2005;**95**:1070–1071.
8. Maron BJ. Sudden death in young athletes. *N Eng J Med* 2003;**349**:1064–1075.
9. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* 1998;**339**:364–369.
10. Pelliccia A, Culasso F, Di Paolo FM, Accettura D, Cantore R, Castagna W, Ciacciarelli A, Costini G, Cuffari B, Drago E, Federici V, Gribaudo CG, Lacovelli G, Landolfi L, Menichetti G, Atzeni UO, Parisi A, Pizzi AR, Rosa M, Santelli F, Santilio F, Vagnini A, Casasco M, Di Luigi L. Prevalence of abnormal electrocardiograms in a large, unselected population undergoing pre-participation cardiovascular screening. *Eur Heart J* 2007;**28**:2006–2010.
11. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes: clinical, demographic, and pathological profiles. *J Am Med Assoc* 1996;**276**:199–204.
12. Ostman-Smith I, Wettrell G, Keeton B, Holmgren D, Ergander U, Gould S, Bowker C, Verdicchio M. Age- and gender-specific mortality rates in childhood hypertrophic cardiomyopathy. *Eur Heart J* 2008;**29**:1160–1167.
13. Friedmann HH. *Diagnostic Electrocardiography and Vecterocardiography*. New York: McGraw-Hill; 1971.
14. Bazzet HC. An analysis of the time relations of electrocardiograms. *Heart* 1920;**7**:353–367.
15. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy obtained by unipolar precordial and limb leads. *Am Heart J* 1949;**37**:161–186.

16. Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two dimensional real time ultrasound imaging of the heart and great vessels: technique, image orientation, structure identification and validation. *Mayo Clin Proc* 1978;**53**:271–303.
17. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Steward WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440–1463.
18. Chan KL, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of 3 Doppler ultrasound methods in the prediction of pulmonary artery pressure. *J Am Coll Cardiol* 1987;**9**:549–554.
19. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**40**:1431–1436.
20. Lewis JF, Spirito P, Pellicia A, Maron BJ. Usefulness of Doppler echocardiographic assessment of diastolic filling in distinguishing 'athlete's heart' from hypertrophic cardiomyopathy. *Br Heart J* 1992;**68**:296–300.
21. Basavarajaiah S, Makan J, Naghavi SH, Whyte G, Gati S, Sharma S. Physiologic upper limits of left atrial diameter in highly trained adolescent athletes. *J Am Coll Cardiol* 2006;**47**:2341–2342.
22. Sen-Chowdhry S, Lowe MD, Sporton SC, McKenna WJ. Arrhythmogenic right ventricular cardiomyopathy: clinical presentation, diagnosis, and management. *Am J Med* 2004;**117**:685–695.
23. Kim YJ, Choi BW, Hur J, Lee HJ, Seo JS, Kim TH, Choe KO, Ha JW. Delayed enhancement in hypertrophic cardiomyopathy: comparison with myocardial tagging MRI. *J Magn Reson Imaging* 2008;**27**:1054–1060.
24. Tandri H, Saranathan M, Rodriguez ER, Martinez C, Bomma C, Nasir K, Rosen B, Lima JA, Calkins H, Bluemke DA. Noninvasive detection of myocardial fibrosis in Arrhythmogenic right ventricular cardiomyopathy using delayed-enhancement magnetic resonance imaging. *J Am Coll Cardiol* 2005;**45**:98–103.
25. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. *Ann Clin Res* 1971;**3**:323–332.
26. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. *Circulation* 1990;**82**:1995–2002.
27. Monseratt L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent risk marker of sudden death in young patients. *J Am Coll Cardiol* 2003;**42**:873–879.
28. Biffi A, Pelliccia A, Verdile L, Fernando F, Spataro A, Caselli S, Santini M, Maron BJ. Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes. *J Am Coll Cardiol* 2002;**40**:446–452.
29. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002;**90**:29–34.
30. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function and mass with cardiovascular magnetic resonance. *Am Heart J* 2004;**147**:218–223.
31. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J* 1994;**71**:215–218.
32. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *J Am Med Assoc* 2002;**287**:1308–1320.
33. Savage DD, Seides SF, Clark CE, Henry WL, Maron BJ, Robinson FC, Epstein SE. Electrocardiographic findings in patients with obstructive and non-obstructive hypertrophic cardiomyopathy. *Circulation* 1978;**58**:402–408.
34. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med* 1988;**318**:129–133.
35. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden death in young competitive athletes after implementation of a preparticipation screening program. *J Am Med Assoc* 2006;**296**:1593–1601.
36. Pelliccia A, Di Paolo FM, Corrado D, Buccolieri C, Quattrini FM, Pisicchio C, Spataro A, Biffi A, Granata M, Maron BJ. Evidence for efficacy of the Italian national pre-participation screening programme for identification of hypertrophic cardiomyopathy in competitive athletes. *Eur Heart J* 2006;**27**:2196–2000.
37. Pellicia A, Maron BJ. Preparticipation cardiovascular evaluation of the competitive athlete: perspectives from the 30-year Italian experience. *Am J Cardiol* 1995;**75**:827–829.
38. Corrado D, Pelliccia A, Bjørnstad HH, Vanhees L, Biffi A, Borjesson M *et al.* Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J* 2005;**26**:516–520.
39. Bille K, Figuiras D, Schamasch P. Sudden cardiac death in athletes. The Lausanne recommendations. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:859–875.
40. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McRoy KL, McDonald MA, Messere JE, Colan SD. The incidence of paediatric cardiomyopathy in two regions of the United States. *N Engl J Med* 2003;**348**:1647–1655.
41. Nugent AW, Daubebey PEF, Chondros P, Carlin JB, Cheung M, Wilkinson LC, Davis AM, Kahler SG, Chow CW, Wilkinson JL, Weintraub RG. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med* 2003;**348**:1639–1646.
42. Pelliccia A, Di Paolo FM, Quattrini FM, Basso C, Culasso F, Popoli G, De Luca R, Spataro A, Biffi A, Thiene G, Maron BJ. Outcomes in athletes with marked ECG repolarization abnormalities. *N Engl J Med* 2008;**358**:152–161.